TITLE

METHOD FOR PREPARING FUSED OXAZINONES

BACKGROUND OF THE INVENTION

A need exists for additional methods for preparing fused oxazinones. Such compounds
include intermediates for the preparation of crop protection agents, pharmaceuticals and
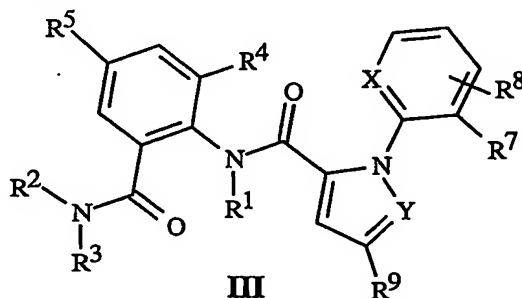other fine chemicals.

Fused oxazinones have been prepared by a variety of methods. For example,
N-acylanthranilic acids have been treated with acetic anhydride, anthranilic acids have been
treated with carboxylic acid anhydrides, and anthranilic acids and carboxylic acids have been
coupled in the presence of various dehydrating agents (see G. M. Coppola, *J. Heterocyclic
Chemistry* **1999**, *36*, 563–588). Fused oxazinones have also been prepared by treatment of
ortho-amino carboxylic acids with carboxylic acid chlorides in the presence of base (see e.g.,
Jakobsen et al., *Biorganic and Medicinal Chemistry* **2000**, *8*, 2803–2812 and Jakobsen et al.,
Biorganic and Medicinal Chemistry **2000**, *8*, 2095–2103). Benzoxazinones have also been
prepared by treatment of a carboxylic acid with a sulfonyl chloride and then treatment with
an anthranilic acid (see D. V. Ramana and E. Kantharaj, *Org. Prep. Proced. Int.* **1993**, *25*,
588).

SUMMARY OF THE INVENTION

This invention provides a method for preparing a fused oxazinone. This method
comprises:

contacting a carboxylic acid with a sulfonyl chloride and an isatoic anhydride in the
presence of a tertiary amine to form the fused oxazinone, the nominal mole ratio of said
sulfonyl chloride to said carboxylic acid being from about 1.0 to 1.5 and the nominal mole
ratio of said isatoic anhydride to said carboxylic acid being from about 0.8 to 1.2.

This invention also relates to a method for preparing a compound of Formula **III**,

III

wherein
    X is N or CR^6;
    Y is N or CH;
    R^1 is H;

R^2 is H or CH_3;

R^3 is C_1-C_6 alkyl;

R^4 is C_1-C_4 alkyl or halogen;

R^5 is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, CN or halogen;

R^6 and R^7 are independently H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, CN or C_1-C_4 haloalkoxy;

R^8 is H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_2-C_4 haloalkenyl, C_2-C_4 haloalkynyl, C_3-C_6 halocycloalkyl, halogen, CN, NO_2, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, C_3-C_6 cycloalkylamino, $(C_1-C_4$ alkyl$)(C_3-C_6$ cycloalkyl$)$amino, C_2-C_4 alkylcarbonyl, C_2-C_6 alkoxycarbonyl, C_2-C_6 alkylaminocarbonyl, C_3-C_8 dialkylaminocarbonyl or C_3-C_6 trialkylsilyl;

R^9 is CF_3, OCF_3, $OCHF_2$, OCH_2CF_3, $S(O)_pCF_3$, $S(O)_pCHF_2$ or halogen; and

p is 0, 1 or 2;

using a compound of Formula **1a**
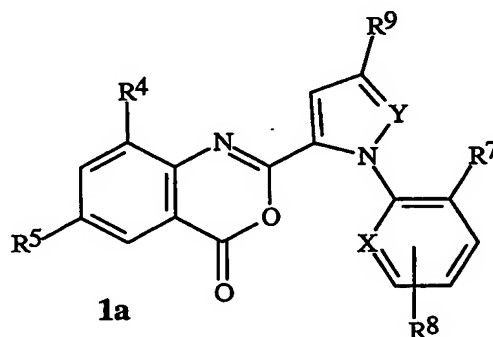
1a

wherein the definitions of X, Y, R^4, R^5, R^7, R^8 and R^9 are the same as for Formula III.

This method is characterized by preparing the compound of Formula **1a** (i.e. a subgenus of Formula **1** described below) by the method as indicated above. Formula **1a** compounds may be prepared using a compound of the formula $LS(O)_2Cl$ (wherein L is selected from alkyl, haloalkyl and phenyl optionally substituted with from one to three substituents independently selected from alkyl or halogen) as the sulfonyl chloride, a compound of Formula **2'** as the carboxylic acid, and a compound of Formula **5'** as the isatoic anhydride

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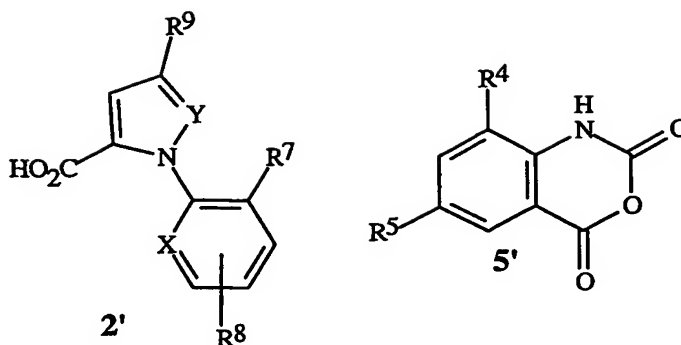
wherein the definitions of X, Y, R^4, R^5, R^7, R^8 and R^9 are the same as for Formula III.

DETAILED DESCRIPTION OF THE INVENTION

One aspect of this invention involves the use of tertiary amines together with sulfonyl chloride compounds to provide advantageous production of fused oxazinones. The tertiary amine is used to facilitate contact of the carboxylic acid with the sulfonyl chloride compound and the isatoic anhydride. The sulfonyl chloride compound is used as a reactant to facilitate coupling of the carboxylic acid with the isatoic anhydride to form the fused oxazinone. The components of the reaction mixture can be combined in various orders, which allows for fewer and simpler operations as compared to previously known processes for the production of oxazinones such as 1. These aspects provide effective production of the fused oxazinone while limiting the amounts of the carboxylic acid, the sulfonyl chloride and the isatoic anhydride that are consumed during the formation of the fused oxazinone. This can be especially important when the carboxylic acid is valuable, complex and/or difficult to obtain, and can reduce production costs as compared to previously known processes by reducing consumption of raw materials and by reducing waste. For example, this invention may be used for preparing a compound of Formula 1
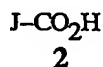

1
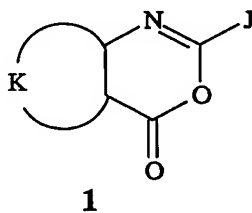
wherein

   J is an optionally substituted carbon moiety; and

   K is, together with the two contiguous linking carbon atoms, a fused phenyl ring or a
       fused 5- or 6-membered heteroaromatic ring, each ring optionally substituted.

More particularly, a compound of Formula 1 can be prepared by a method comprising: contacting a carboxylic acid of Formula 2
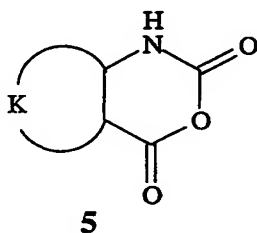
$$J-CO_2H$$

2

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with a sulfonyl chloride of Formula **4**

$$LS(O)_2Cl$$

4

wherein L is selected from alkyl, haloalkyl, and phenyl optionally substituted with from one
to three substituents independently selected from alkyl or halogen; and

5   with an isatoic anhydride of Formula **5**

5

;

in the presence of a tertiary amine.

In the recitations herein, the term "tertiary amines" include trisubstituted amines,
wherein the three substituents of the nitrogen are the same or different carbon moieties, and
10   optionally substituted heteroaromatic amines. Examples of "trisubstituted amines" include
triethylamine, *N,N*-diisopropylethylamine and *N,N*-dimethylaniline.   The optionally
substituted heteroaromatic amines include, but are not limited to, optionally substituted
pyridines, quinoline and pyrimidines and 1,8-diazabicyclo[5.4.0]undec-7-ene.   "Carbon
moiety" refers to a radical in which a carbon atom is connected to the backbone of the fused
15   oxazinone ring of Formula **1** and the carboxylic acid group of Formula **2**. As the carbon
moiety L is separated from the reaction center, it can encompass a great variety of carbon-
based moieties that can be prepared by modern methods of synthetic organic chemistry. The
method of this invention is generally applicable to prepare a wide range of compounds of
Formula **1**.

20   "Carbon moiety" thus includes alkyl, alkenyl and alkynyl moieties, which can be
straight-chain or branched.

"Carbon moiety" also includes carbocyclic and heterocyclic rings, which can be
saturated, partially saturated, or completely unsaturated. The carbocyclic and heterocyclic
rings of a carbon moiety group can form polycyclic ring systems comprising multiple rings
25   connected together. The term "carbocyclic ring" denotes a ring wherein the atoms forming
the ring backbone are selected only from carbon. "Saturated carbocyclic" refers to a ring
having a backbone consisting of carbon atoms linked to one another by single bonds; unless
otherwise specified, the remaining carbon valences are occupied by hydrogen atoms. The
term "hetero" in connection with rings or ring systems refers to a ring or ring system in
30   which at least one ring atom is not carbon and which can contain from one to four

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heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur, provided that each ring contains no more than 4 nitrogens, no more than 2 oxygens and no more than 2 sulfurs. When the carbon moiety consists of a heterocyclic ring or ring system, it is connected to the backbone of the fused oxazinone ring of Formula 1 and the

5   carboxylic acid group of Formula 2 through any available carbon ring atom by replacement of a hydrogen on said carbon atom. Heterocyclic rings or ring systems may also be connected to the carbon moiety through any available carbon or nitrogen atom by replacement of a hydrogen on said carbon or nitrogen atom.

Although there is no definite limit to the size of Formula 1 suitable for the process of

10   the invention, typically Formula 1 comprises 9–100, more commonly 9–50, and most commonly 9–25 carbon atoms, and 3–25, more commonly 3–15, and most commonly 3–10 heteroatoms. Heteroatoms are atoms other than carbon or hydrogen and are commonly selected from halogen, oxygen, sulfur, nitrogen, phosphorus and silicon. Three heteroatoms in Formula 1 are the nitrogen atom and the two oxygen atoms in the oxazinone moiety.

15   When K is a fused heteroaromatic ring or when the carbon moiety comprises a heterocyclic ring, additional heteroatoms are contained therein. Substituents attached to the K ring or the carbon moiety may also contain additional heteroatoms.

Unsaturated rings can be aromatic if Hückel's rule is satisfied. "Aromatic" indicates that each of the ring atoms is essentially in the same plane and has a p-orbital perpendicular

20   to the ring plane, and in which $(4n + 2)$ π electrons, when n is 0 or a positive integer, are associated with the ring to comply with Hückel's rule. The term "aromatic ring system" denotes fully unsaturated carbocycles and heterocycles in which at least one ring of a polycyclic ring system is aromatic. The term "aromatic carbocyclic ring or ring system" includes fully aromatic carbocycles and carbocycles in which at least one ring of a

25   polycyclic ring system is aromatic (e.g., phenyl, naphthyl and 1,2,3,4-tetrahydro-naphthalenyl). The term "nonaromatic carbocyclic ring or ring system" denotes fully saturated carbocycles as well as partially or fully unsaturated carbocycles where the Hückel rule is not satisfied by any of the rings in the ring system. The terms "heteroaromatic ring or ring system" and "aromatic fused heterobicyclic ring system" includes fully aromatic

30   heterocycles and heterocycles in which at least one ring of a polycyclic ring system is aromatic (where aromatic indicates that the Hückel rule is satisfied). The term "nonaromatic heterocyclic ring or ring system" denotes fully saturated heterocycles as well as partially or fully unsaturated heterocycles where the Hückel rule is not satisfied by any of the rings in the ring system. The term "aryl" denotes a carbocyclic or heterocyclic ring or ring system in

35   which at least one ring is aromatic, and the aromatic ring provides the connection to the remainder of the molecule.

The carbon moiety specified for J is optionally substituted. Also, the K ring moieties of Formulae 1 and 5 are optionally substituted. Furthermore, the tertiary amines can be

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optionally substituted heteroaromatic amines. The term "optionally substituted" in connection with these groups refers to groups that are unsubstituted or have at least one non-hydrogen substituent. Illustrative optional substituents include alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, hydroxycarbonyl, formyl, alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkoxycarbonyl, hydroxy, alkoxy, alkenyloxy, alkynyloxy, cycloalkoxy, aryloxy, alkylthio, alkenylthio, alkynylthio, cycloalkylthio, arylthio, alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, cycloalkylsulfinyl, arylsulfinyl, alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, amino, alkylamino, alkenylamino, alkynylamino, arylamino, aminocarbonyl, alkylaminocarbonyl, alkenyl-aminocarbonyl, alkynylaminocarbonyl, arylaminocarbonyl, alkylaminocarbonyl, alkenyl-aminocarbonyl, alkynylaminocarbonyl, arylaminocarbonyloxy, alkoxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino and aryloxycarbonylamino, silyl moieties and siloxy moieties, each further optionally substituted; halogen; cyano; and nitro. The optional further substituents are independently selected from groups like those illustrated above for the substituents themselves to give additional substituent groups for J and K such as haloalkyl, haloalkenyl and haloalkoxy. As another example, alkylamino can be further substituted with alkyl, giving dialkylamino. The substituents can also be tied together by figuratively removing one or two hydrogen atoms from each of two substituents or a substituent and the supporting molecular structure and joining the radicals to produce cyclic and polycyclic structures fused or appended to the molecular structure supporting the substituents. For example, tying together adjacent hydroxy and methoxy groups attached to, for example, a phenyl ring gives a fused dioxolane structure containing the linking group -O-CH$_2$-O-. Tying together a hydroxy group and the molecular structure to which it is attached can give cyclic ethers, including epoxides. Illustrative substituents also include oxygen, which when attached to carbon forms a carbonyl function or when attached to nitrogen forms an N-oxide.

One skilled in the art will appreciate that not all nitrogen-containing heterocycles can form N-oxides since the nitrogen requires an available lone pair for oxidation to the oxide; one skilled in the art will recognize those nitrogen containing heterocycles which can form N-oxides. One skilled in the art will also recognize that tertiary amines can form N-oxides. Synthetic methods for the preparation of N-oxides of heterocycles and tertiary amines are very well known by one skilled in the art including the oxidation of heterocycles and tertiary amines with peroxy acids such as peracetic and m-chloroperbenzoic acid (MCPBA), hydrogen peroxide, alkyl hydroperoxides such as t-butyl hydroperoxide, sodium perborate, and dioxiranes such as dimethyldioxirane. These methods for the preparation of N-oxides have been extensively described and reviewed in the literature, see for example: T. L. Gilchrist in *Comprehensive Organic Synthesis*, vol. 7, pp 748–750, S. V. Ley, Ed., Pergamon Press; M. Tisler and B. Stanovnik in *Comprehensive Heterocyclic Chemistry*, vol.

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3, pp 18–20, A. J. Boulton and A. McKillop, Eds., Pergamon Press; M. R. Grimmett and
B. R. T. Keene in *Advances in Heterocyclic Chemistry*, vol. *43*, pp 149–161, A. R. Katritzky,
Ed., Academic Press; M. Tisler and B. Stanovnik in *Advances in Heterocyclic Chemistry*,
vol. *9*, pp 285–291, A. R. Katritzky and A. J. Boulton, Eds., Academic Press; and
5   G. W. H. Cheeseman and E. S. G. Werstiuk in *Advances in Heterocyclic Chemistry*, vol. *22*,
pp 390–392, A. R. Katritzky and A. J. Boulton, Eds., Academic Press.

As referred to herein, "alkyl", used either alone or in compound words such as
"alkylthio" or "haloalkyl" includes straight-chain or branched alkyl, such as, methyl, ethyl,
n-propyl, *i*-propyl, and the different butyl, pentyl or hexyl isomers. "Alkenyl" includes
10   straight-chain or branched alkenes such as ethenyl, 1-propenyl, 2-propenyl, and the different
butenyl, pentenyl and hexenyl isomers. "Alkenyl" also includes polyenes such as
1,2-propadienyl and 2,4-hexadienyl. "Alkynyl" includes straight-chain or branched alkynes
such as ethynyl, 1-propynyl, 2-propynyl and the different butynyl, pentynyl and hexynyl
isomers. "Alkynyl" can also include moieties comprised of multiple triple bonds such as
15   2,5-hexadiynyl. "Alkoxy" includes, for example, methoxy, ethoxy, *n*-propyloxy,
isopropyloxy and the different butoxy, pentoxy and hexyloxy isomers. "Alkenyloxy"
includes straight-chain or branched alkenyloxy moieties. Examples of "alkenyloxy" include
$H_2C=CHCH_2O$, $(CH_3)_2C=CHCH_2O$, $(CH_3)CH=CHCH_2O$, $(CH_3)CH=C(CH_3)CH_2O$ and
$CH_2=CHCH_2CH_2O$. "Alkynyloxy" includes straight-chain or branched alkynyloxy
20   moieties. Examples of "alkynyloxy" include $HC\equiv CCH_2O$, $CH_3C\equiv CCH_2O$ and
$CH_3C\equiv CCH_2CH_2O$. "Alkylthio" includes branched or straight-chain alkylthio moieties
such as methylthio, ethylthio, and the different propylthio, butylthio, pentylthio and
hexylthio isomers. "Alkylsulfinyl" includes both enantiomers of an alkylsulfinyl group.
Examples of "alkylsulfinyl" include $CH_3S(O)$, $CH_3CH_2S(O)$, $CH_3CH_2CH_2S(O)$,
25   $(CH_3)_2CHS(O)$ and the different butylsulfinyl, pentylsulfinyl and hexylsulfinyl isomers.
Examples of "alkylsulfonyl" include $CH_3S(O)_2$, $CH_3CH_2S(O)_2$, $CH_3CH_2CH_2S(O)_2$,
$(CH_3)_2CHS(O)_2$ and the different butylsulfonyl, pentylsulfonyl and hexylsulfonyl isomers.
"Alkylamino", "alkenylthio", "alkenylsulfinyl", "alkenylsulfonyl", "alkynylthio",
"alkynylsulfinyl", "alkynylsulfonyl", and the like, are defined analogously to the above
30   examples. Examples of "alkylcarbonyl" include $C(O)CH_3$, $C(O)CH_2CH_2CH_3$ and
$C(O)CH(CH_3)_2$. Examples of "alkoxycarbonyl" include $CH_3OC(=O)$, $CH_3CH_2OC(=O)$,
$CH_3CH_2CH_2OC(=O)$, $(CH_3)_2CHOC(=O)$ and the different butoxy- or pentoxycarbonyl
isomers. "Cycloalkyl" includes, for example, cyclopropyl, cyclobutyl, cyclopentyl,
cyclohexyl, cycloheptyl and cyclooctyl. The term "cycloalkoxy" includes the same groups
35   linked through an oxygen atom such as cyclopentyloxy and cyclohexyloxy.
"Cycloalkylamino" means the amino nitrogen atom is attached to a cycloalkyl radical and a
hydrogen atom and includes groups such as cyclopropylamino, cyclobutylamino,
cyclopentylamino and cyclohexylamino. "(Alkyl)(cycloalkyl)amino" (or

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"(alkyl)cycloalkylamino") means a cycloalkylamino group where the hydrogen atom is replaced by an alkyl radical; examples include groups such as (methyl)(cyclopropyl)amino, (butyl)(cyclobutyl)amino, (propyl)cyclopentylamino, (methyl)cyclohexylamino and the like. "Cycloalkenyl" includes groups such as cyclopentenyl and cyclohexenyl as well as groups with more than one double bond such as 1,3- and 1,4-cyclohexadienyl.

The term "halogen", either alone or in compound words such as "haloalkyl", includes fluorine, chlorine, bromine or iodine. Further, when used in compound words such as "haloalkyl", said alkyl may be partially or fully substituted with halogen atoms which may be the same or different. Examples of "haloalkyl" include F_3C, $ClCH_2$, CF_3CH_2 and CF_3CCl_2.

The term "silyl moieties" refers to moieties containing at least one silicon atom bonded to the remainder of Formula 1 through said silicon atom and includes groups such as trialkylsilyl (examples include trimethylsilyl, triisopropylsilyl and dimethyl-t-butylsilyl) and dialkylarylsilyl groups (e.g. dimethylphenylsilyl). The term "siloxy moieties" refers to moieties containing at least one silicon atom bonded to an oxygen atom and connected to the remainder of Formula 1 through said oxygen atom and includes groups such as trialkylsiloxy (examples include trimethylsiloxy, triisopropylsiloxy and dimethyl-t-butylsiloxy) and dialkylarylsilyl groups (e.g. dimethylphenylsiloxy).
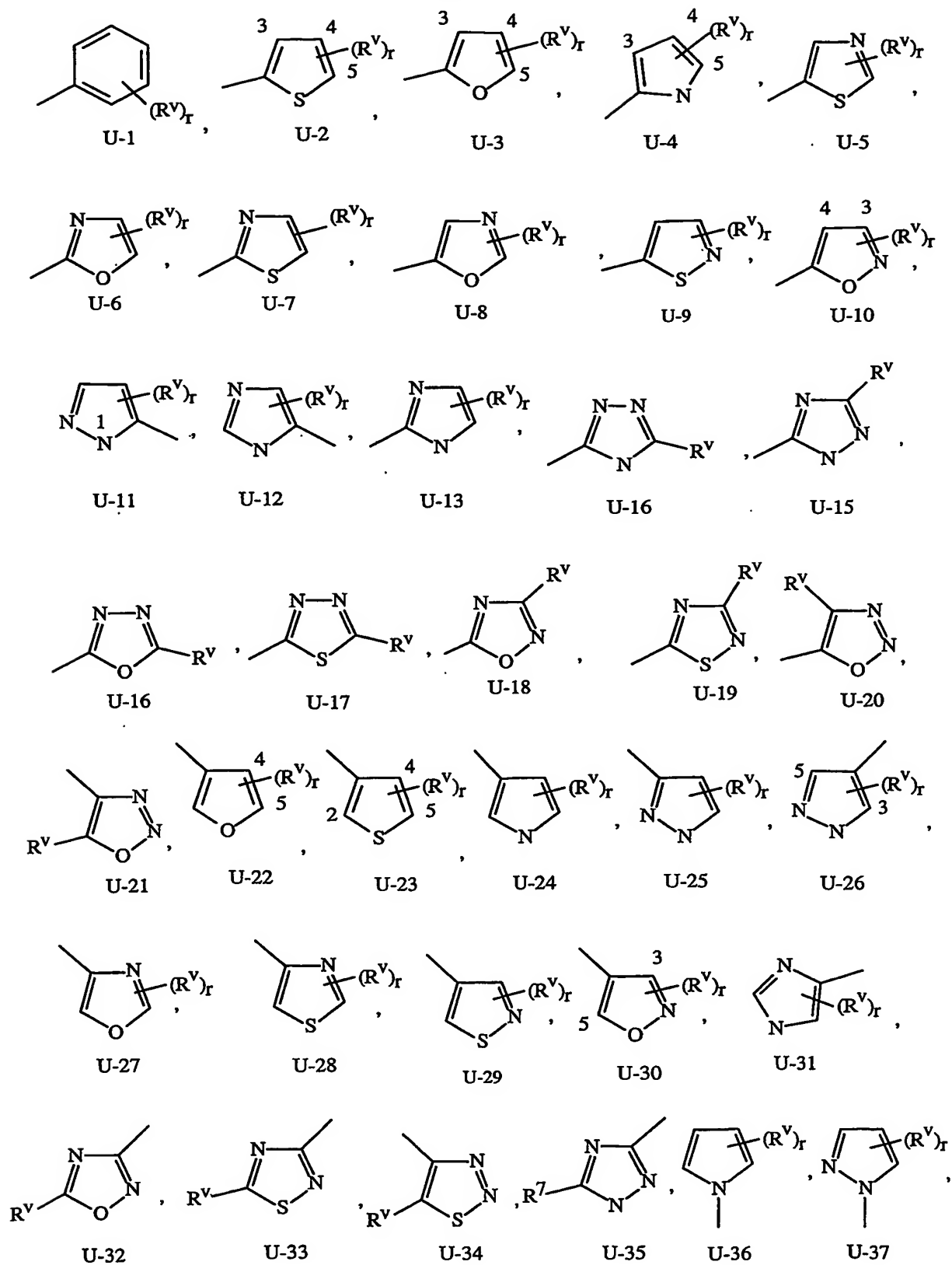
The total number of carbon atoms in a substituent group is indicated by the "C_i–C_j" prefix where i and j are, for example, numbers from 1 to 3; e.g., C_1–C_3 alkyl designates methyl through propyl.

Of note as tertiary amines are optionally substituted pyridines. There is no definite limit to the nature and size of the substituents on the pyridine, but the substituents are commonly alkyl, more particularly C_1–C_6, more commonly C_1–C_4, and most commonly C_1 (i.e. methyl). Typical examples of optionally substituted pyridines are pyridine, the picolines (i.e. 2-methylpyridine, 3-methylpyridine, 4-methylpyridine), the lutidines (e.g., 2,3-dimethylpyridine, 2,4-dimethylpyridine, 2,5-dimethylpyridine, 2,5-dimethylpyridine, 3,4-dimethylpyridine, 3,5-dimethylpyridine) and collidine. Other common substituents are dimethylamino (e.g., 4-(dimethylamino)pyridine) and pyrrolidino (e.g., 4-(pyrrolidino)pyridine). Furthermore, two substituents on pyridine can be tied together as already described to form other common pyridine derivatives, such as quinoline and isoquinoline. These quinoline and isoquinoline pyridine derivatives can also be further substituted.

Although there is no definite limit to the size of J, optionally substituted alkyl moieties in J commonly include 1 to 6 carbon atoms, more commonly 1 to 4 carbon atoms, and most commonly 1 or 2 carbon atoms in the alkyl chain. Similarly, optionally substituted alkenyl and alkynyl moieties in J commonly include 2 to 6 carbon atoms, more commonly 2 to 4 carbon atoms, and most commonly 2 or 3 carbon atoms in the alkenyl or alkynyl chain.

As indicated above, the carbon moiety J may be (among others) an aromatic ring or ring system. Examples of aromatic rings or ring systems include a phenyl ring, 5- or 6-membered heteroaromatic rings, aromatic 8-, 9- or 10-membered fused carbobicyclic ring systems and aromatic 8-, 9- or 10-membered fused heterobicyclic ring systems, wherein each

5   ring or ring system is optionally substituted. The term "optionally substituted" in connection with these J groups refers to groups that are unsubstituted or have at least one non-hydrogen substituent. These carbon moieties may be substituted with as many optional substituents as can be accommodated by replacing a hydrogen atom with a non-hydrogen substituent on any available carbon or nitrogen atom. Commonly, the number of optional substituents (when

10 present) ranges from one to four. An example of phenyl optionally substituted with from one to four substituents is the ring illustrated as U-1 in Exhibit 1, wherein R^v is any substituent and r is an integer from 0 to 4. Examples of aromatic 8-, 9- or 10-membered fused carbobicyclic ring systems optionally substituted with from one to four substituents include a naphthyl group optionally substituted with from one to four substituents illustrated

15 as U-85 and a 1,2,3,4-tetrahydronaphthyl group optionally substituted with from one to four substituents illustrated as U-86 in Exhibit 1, wherein R^v is any substituent r is an integer from 0 to 4. Examples of 5- or 6-membered heteroaromatic rings optionally substituted with from one to four substituents include the rings U-2 through U-53 illustrated in Exhibit 1 wherein R^v is any substituent and r is an integer from 0 to 4. Examples of aromatic 8-, 9- or

20 10-membered fused heterobicyclic ring systems optionally substituted with from one to four substituents include U-54 through U-84 illustrated in Exhibit 1 wherein R^v is any substituent and r is an integer from 0 to 4. Other examples of J include a benzyl group optionally substituted with from one to four substituents illustrated as U-87 and a benzoyl group optionally substituted with from one to four substituents illustrated as U-88 in Exhibit 1,

25 wherein R^v is any substituent and r is an integer from 0 to 4.

Although R^v groups are shown in the structures U-1 through U-88, it is noted that they do not need to be present since they are optional substituents. The nitrogen atoms that require substitution to fill their valence are substituted with H or R^v. Note that some U groups can only be substituted with less than 4 R^v groups (e.g. U-14, U-15, U-18 through

30 U-21 and U-32 through U-34 can only be substituted with one R^v). Note that when the attachment point between $(R^v)_r$ and the U group is illustrated as floating, $(R^v)_r$ can be attached to any available carbon atom or nitrogen atom of the U group. Note that when the attachment point on the U group is illustrated as floating, the U group can be attached to the remainder of Formula I through any available carbon of the U group by replacement of a

35 hydrogen atom.

Exhibit 1

U-1, U-2, U-3, U-4, U-5,

U-6, U-7, U-8, U-9, U-10,

U-11, U-12, U-13, U-16, U-15,

U-16, U-17, U-18, U-19, U-20,

U-21, U-22, U-23, U-24, U-25, U-26,

U-27, U-28, U-29, U-30, U-31,

U-32, U-33, U-34, U-35, U-36, U-37,

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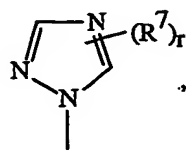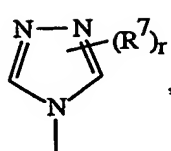
U-38 , U-39 , U-40 , U-41 , U-42 ,
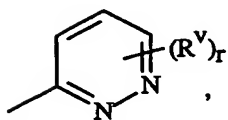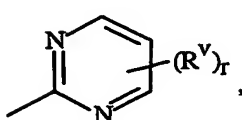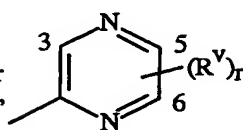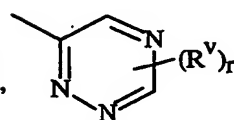
U-43 , U-44 , U-45 , U-46 , U-47 ,
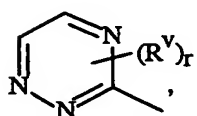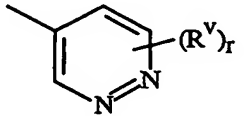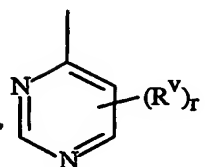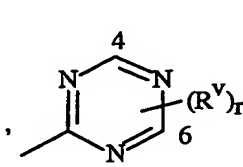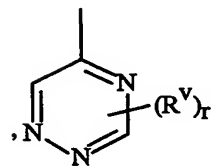
U-48 , U-49 , U-50 , U-51 , U-52 ,
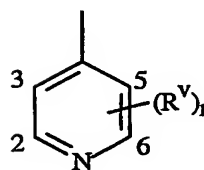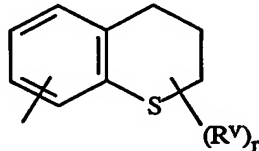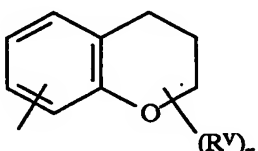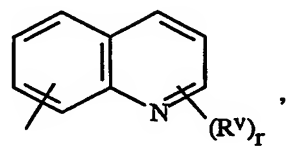
U-53 , U-54 , U-55 , U-56 ,
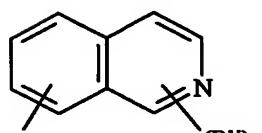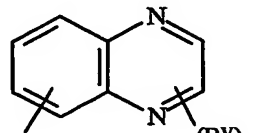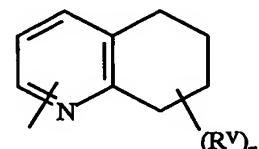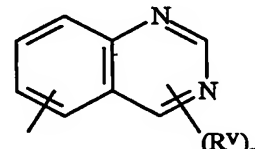
U-57 , U-58 , U-59 , U-60 ,
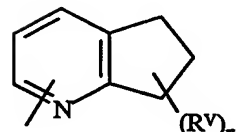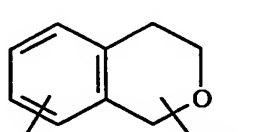
U-61 , U-62 , U-63 , U-64 ,

U-65 , U-66 , U-67 , U-68 ,

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U-69 , U-70 , U-71 , U-72 ,

U-73 , U-74 , U-75 , U-76 ,

U-77 , U-78 , U-79 , U-80 ,

U-81 , U-82 , U-83 , U-84 ,

U-85 , U-86 , U-87 or U-88 .
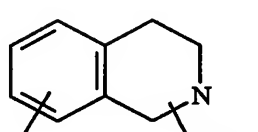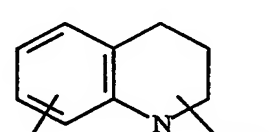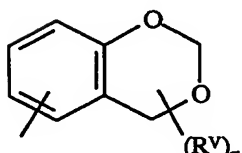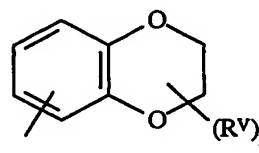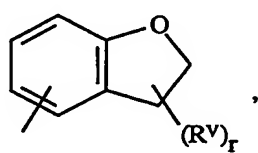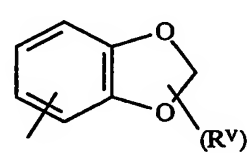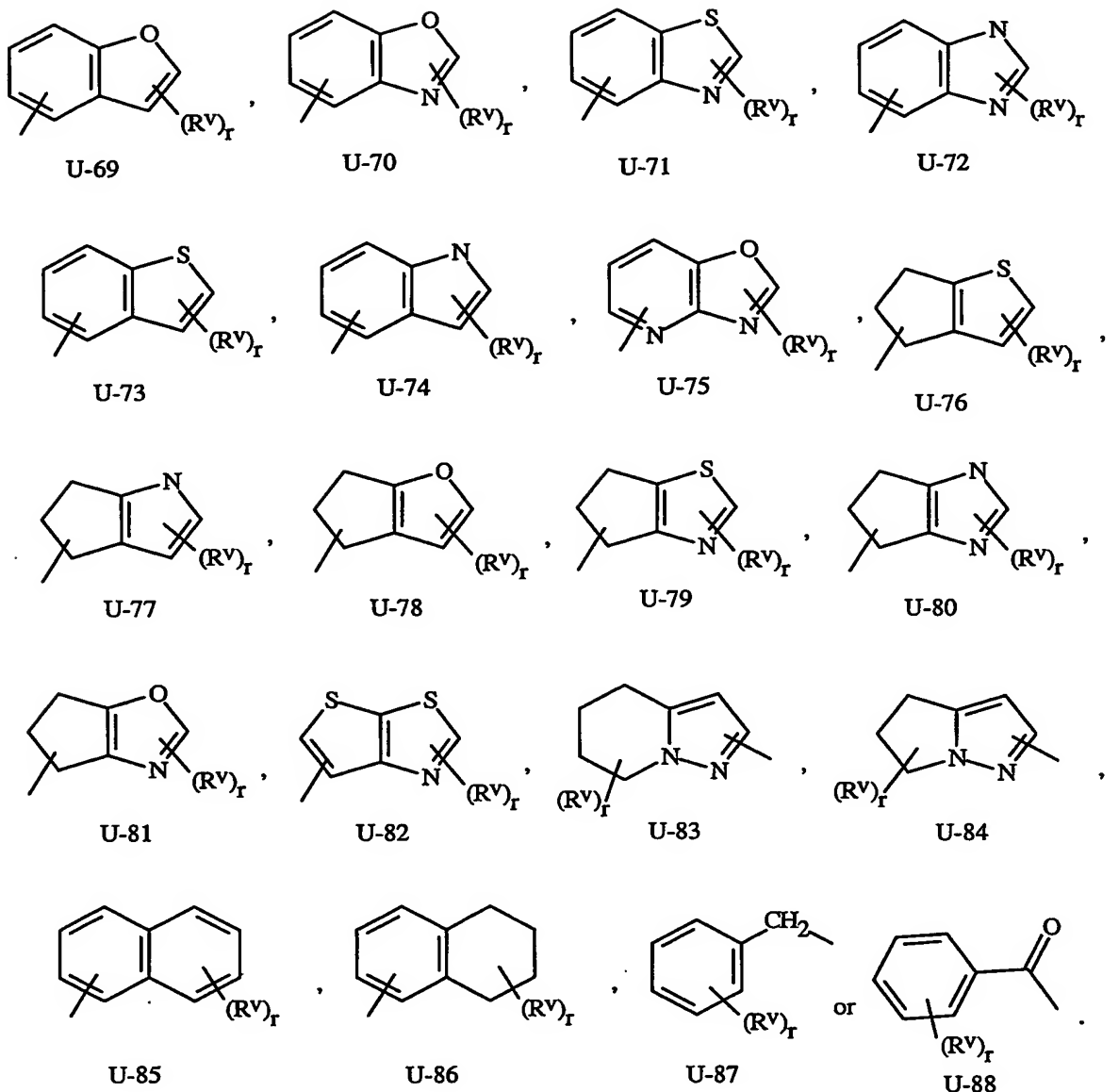
As indicated above, the carbon moiety J may be (among others) saturated or partially

5   saturated carbocyclic and heterocyclic rings, which can be further optionally substituted.
The term "optionally substituted" in connection with these J groups refers to groups that are
unsubstituted or have at least one non-hydrogen substituent. These carbon moieties may be
substituted with as many optional substituents as can be accommodated by replacing a
hydrogen atom with a non-hydrogen substituent on any available carbon or nitrogen atom.

10   Commonly, the number of optional substituents (when present) ranges from one to four.
Examples of saturated or partially saturated carbocyclic rings include optionally substituted
C_3–C_8 cycloalkyl and optionally substituted C_3–C_8 cycloalkenyl. Examples of saturated or
partially saturated heterocyclic rings include optionally substituted 5- or 6-membered
nonaromatic heterocyclic rings optionally including one or two ring members selected from

15   the group consisting of C(=O), SO or S(O)$_2$. Examples of such J groups include those

illustrated as G-1 through G-35 in Exhibit 2. Note that when the attachment point on these G groups is illustrated as floating, the G group can be attached to the remainder of Formula 1 through any available carbon or nitrogen of 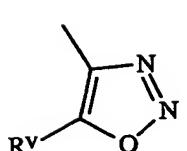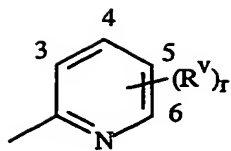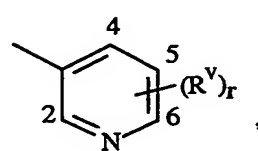the G group by replacement of a hydrogen atom. The optional substituents can be attached to any available carbon or nitrogen by replacing a hydrogen atom (said substituents are not illustrated in Exhibit 2 since they are optional substituents). Note that when G comprises a ring selected from G-24 through G-31, G-34 and G-35, Q^2 may be selected from O, S, NH or substituted N.

<div align="center"><u>Exhibit 2</u></div>

G-1, G-2, G-3, G-4, G-5, G-6,

G-7, G-8, G-9, G-10, G-11, G-12,

G-13, G-14, G-15, G-16, G-17, G-18,

G-19, G-20, G-21, G-22, G-23, G-24,

G-25, G-26, G-27, G-28, G-29, G-30

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G-31   G-32   ,   G-33   ,   G-34   and   G-35   .
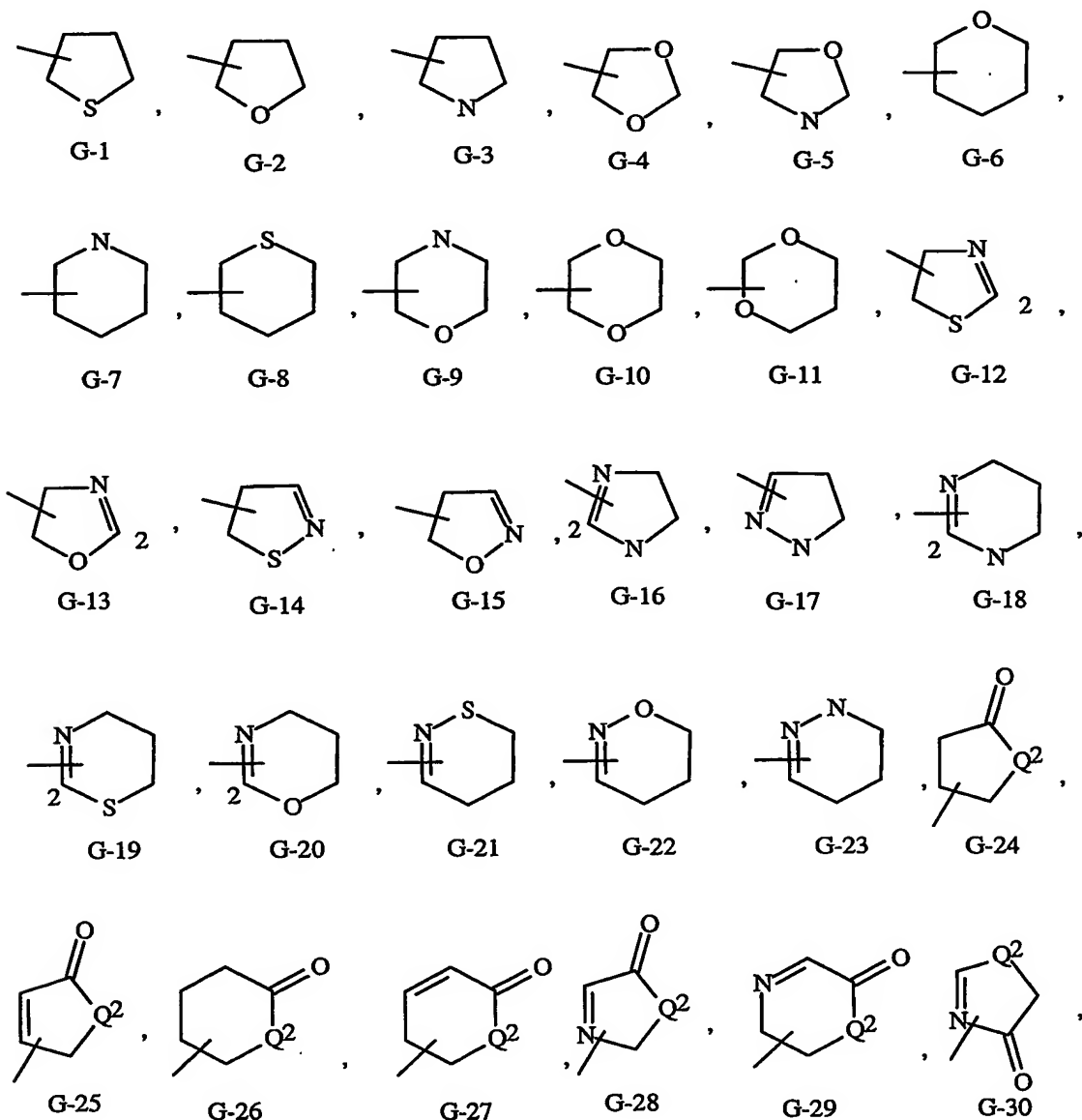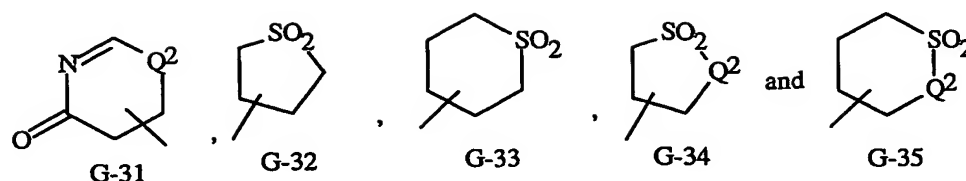
It is noted that the J group may be optionally substituted. As noted above, a J group may commonly comprise a U group or a G group further substituted with from one to four substituents. Thus J groups may comprise a U group or a G group selected from U-1 through U-88 or G-1 through G-35, and further substituted with additional substituents

5   including from one to four U or G groups (which may be the same or different) and both the core U or G group and substituent U or G groups optionally further substituted. Of note are J groups comprising a U or G group substituted with one U or G group and optionally substituted with from one to three additional substituents. For example, J can be U-11, in which an R^v attached to the 1-nitrogen is the group U-41.

U-11

U-41

10

As noted above, K is, together with the two contiguous linking carbon atoms, a fused phenyl ring or a fused 5- or 6-membered heteroaromatic ring, each ring optionally substituted. The term "optionally substituted" in connection with these K rings refers to K rings that are unsubstituted or have at least one non-hydrogen substituent. An example of a

15 K ring wherein the K ring is optionally substituted with from one to four R^t includes the ring system illustrated as K-38 (fused phenyl ring) in Exhibit 3 wherein n is an integer from 0 to 4 and R^t is any substituent. Examples of said K rings wherein the K ring is optionally substituted with from one to three R^t include the ring systems K-1 to K-37 (5- or 6-membered heteroaromatic rings) in Exhibit 3, wherein n is an integer from 0 to 3 and R^t is

20 any substituent. As with the carbon atoms in the ring, the nitrogen atoms that require substitution to fill their valence are substituted with hydrogen or with R^t. Although $(R^t)_n$ groups are shown in the structures K-1 to K-38, it is noted that R^t does not need to be present since it is an optional substituent. Note that some K rings can only be substituted with less than 3 R^t groups (e.g. K-7 through K-10, K-15, K-16, K-20, K-21, K-23, K-24, K-26 and

25 K-27 can only be substituted with one R^t). In the exemplified K groups, the upper right bond is attached through the available linking carbon atom to the nitrogen atom of the oxazinone portion of Formula 1 and the lower right bond is attached through the available

linking carbon atom to the carbonyl atom of the oxazinone portion of Formula **1**. The wavy line indicates that the K ring is attached to the remainder of Formula **1** as illustrated below.

1

<u>Exhibit 3</u>

K-1   K-2   K-3   K-4

K-5   K-6   K-7   K-8

K-9   K-10   K-11   K-12

K-13   K-14   K-15   K-16

K-17   K-18   K-19   K-20   K-21

16

K-22   K-23   K-24   K-25   K-26   K-27

K-28   K-29   K-30   K-31

K-32   K-33   K-34   K-35

K-36   K-37   and   K-38
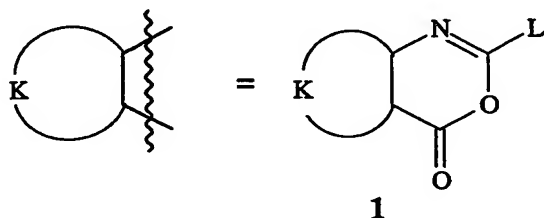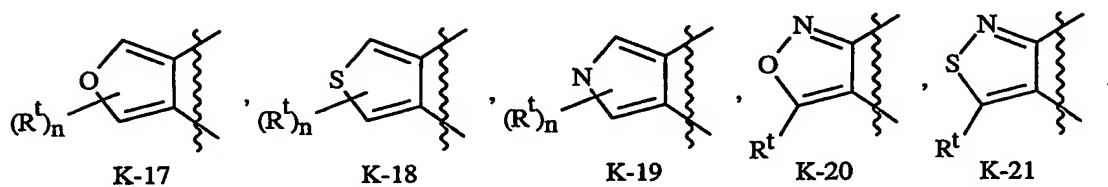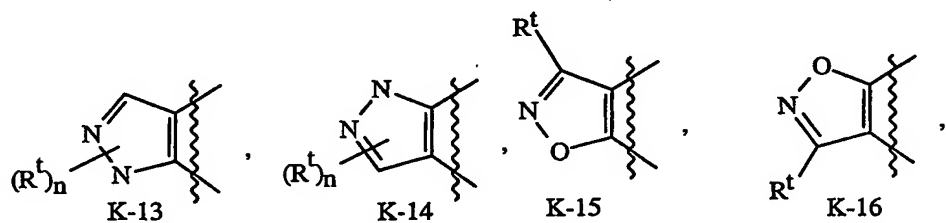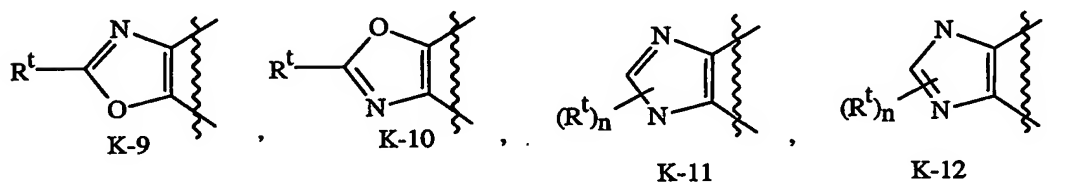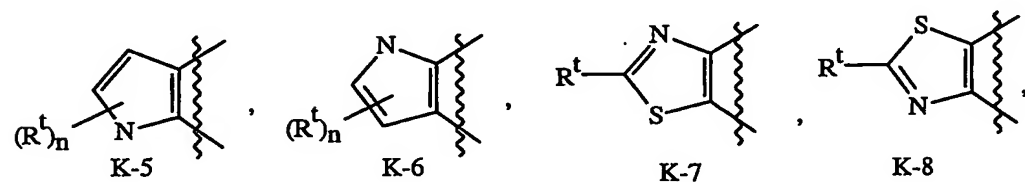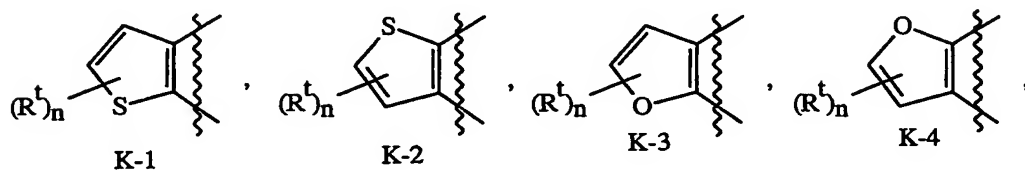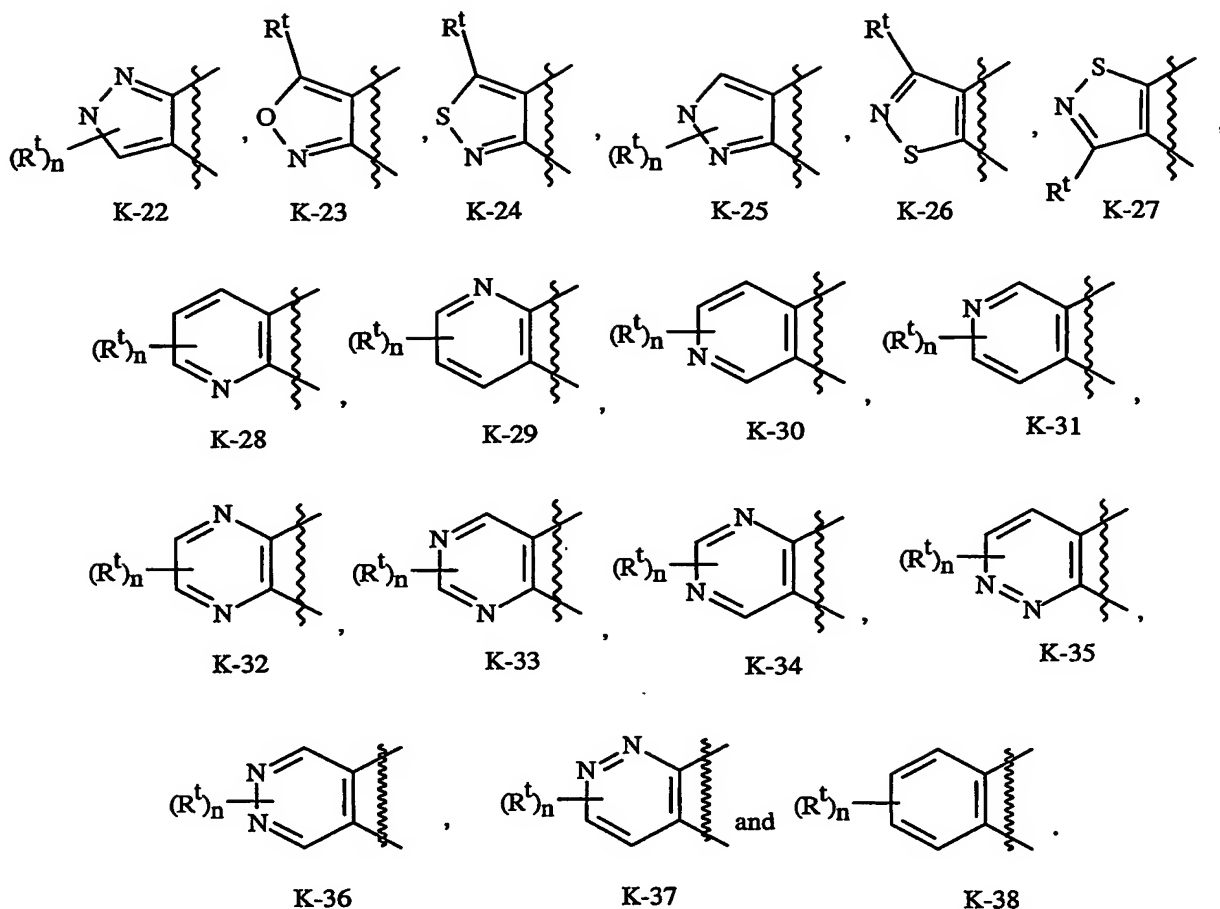
Of note are K rings including optionally substituted thiophene, isoxazole, isothiazole, pyrazole, pyridine and pyrimidine rings. Of particular note are K rings K-1, K-14, K-15, K-18, K-23, K-28, K-29, K-30, K-31 and K-33, especially K-28, K-31 and K-33. Also of particular note is K-38 (optionally substituted phenyl).

Examples of optional substituents that can be attached to the U, G or K groups illustrated above include substituents selected from W. The K rings may also be substituted with the previously described optionally substituted U or optionally substituted G groups.

Each W is independently C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, C_3–C_6 cycloalkyl, C_1–C_4 haloalkyl, C_2–C_4 haloalkenyl, C_2–C_4 haloalkynyl, C_3–C_6 halocycloalkyl, halogen, CN, NO_2, C_1–C_4 alkoxy, C_1–C_4 haloalkoxy, C_1–C_4 alkylthio, C_1–C_4 alkylsulfinyl, C_1–C_4 alkylsulfonyl, C_1–C_4 alkylamino, C_2–C_8 dialkylamino, C_3–C_6 cycloalkylamino, (C_1–C_4 alkyl)(C_3–C_6 cycloalkyl)amino or C_3–C_6 trialkylsilyl.

Other suitable substituents include

$B(OR^{17})_2$; NH_2; SH; thiocyanato; C_3–C_8 trialkylsilyloxy; C_1–C_4 alkyldisulfide; SF_5; $R^{19}C(=E)$-; $R^{19}C(=E)M$-; $R^{19}MC(=E)$-; $(R^{19})MC(=E)M$-; $-OP(=Q)(OR^{19})_2$; $-S(O)_2MR^{19}$; $R^{19}S(O)_2M$-;

wherein

each E is independently O, S, NR^{15}, NOR^{15}, $NN(R^{15})_2$, N-S=O, N-CN or N-NO_2;

each M is independently O, NR^{18} or S;

Q is O or S;

each R^{15} and each R^{19} is independently H; C_1–C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of CN, NO_2, hydroxy, C_1–C_4 alkoxy, C_1–C_4 haloalkoxy, C_1–C_4 alkylthio, C_1–C_4 alkylsulfinyl, C_1–C_4 alkylsulfonyl, C_1–C_4 haloalkylthio, C_1–C_4 haloalkylsulfinyl, C_1–C_4 haloalkylsulfonyl, C_1–C_4 alkylamino, C_2–C_8 dialkylamino, CO_2H, C_2–C_6 alkoxycarbonyl, C_2–C_6 alkylcarbonyl, C_3–C_6 trialkylsilyl, and a phenyl ring optionally substituted with one to three substituents independently selected from W; C_1–C_6 haloalkyl; C_3–C_6 cycloalkyl; or a phenyl ring optionally substituted with from one to three substituents independently selected from W;

each R^{17} is independently H or C_1–C_4 alkyl; or

$B(OR^{17})_2$ can form a ring wherein the two oxygen atoms are linked by a chain of two to three carbons optionally substituted with one or two substituents independently selected from methyl or C_2–C_6 alkoxycarbonyl; and

each R^{18} is independently H, C_1–C_6 alkyl or C_1–C_6 haloalkyl.

Of note are methods for preparing compounds of Formula 1 wherein J is C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_3–C_8 cycloalkyl or C_3–C_8 cycloalkenyl, each optionally substituted; or J is a phenyl ring, a benzyl group, a benzoyl group, a 5- or 6-membered heteroaromatic ring, an aromatic 8-, 9- or 10-membered fused carbobicyclic ring system, an aromatic 8-, 9- or 10-membered fused heterobicyclic ring system or a 5- or 6-membered nonaromatic heterocyclic ring optionally including one or two ring members selected from the group consisting of C(=O), SO or S(O)$_2$, each optionally substituted. Of particular note are such methods wherein
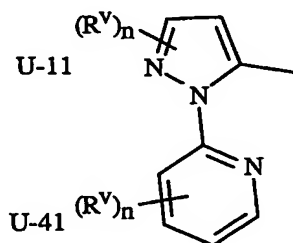
K is, together with the two contiguous linking carbon atoms, a fused phenyl ring optionally substituted with from one to four substituents independently selected from G, U, W or R^{13}; or a fused 5- or 6-membered heteroaromatic ring optionally substituted with from one to three substituents independently selected from G, U, W or R^{13};

J is C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_3–C_8 cycloalkyl or C_3–C_8 cycloalkenyl, each optionally substituted with one or more substituents selected from the group consisting of R^{12}, halogen, CN, NO_2, hydroxy, C_1–C_4 alkoxy, C_1–C_4 alkylsulfinyl, C_1–C_4 alkylsulfonyl, C_1–C_4 alkylamino, C_2–C_8 dialkylamino, C_3–C_6 cycloalkylamino and (C_1–C_4 alkyl)(C_3–C_6 cycloalkyl)amino; or

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J is a phenyl ring, a benzyl group, a benzoyl group, a 5- or 6-membered heteroaromatic ring, an aromatic 8-, 9- or 10-membered fused carbobicyclic ring system, an aromatic 8-, 9- or 10-membered fused heterobicyclic ring system or a 5- or 6-membered nonaromatic heterocyclic ring optionally including one or two ring members selected from the group consisting of $C(=O)$, SO or $S(O)_2$, each optionally substituted with from one to four substituents independently selected from G, U, W or R^{13};

each G is a 5- or 6-membered nonaromatic heterocyclic ring optionally including one or two ring members selected from the group consisting of $C(=O)$, SO or $S(O)_2$, each optionally substituted with from one to four substituents independently selected from W;

each U is a phenyl ring, a benzyl group, a benzoyl group, a 5- or 6-membered heteroaromatic ring, an aromatic 8-, 9- or 10-membered fused carbobicyclic ring system, an aromatic 8-, 9- or 10-membered fused heterobicyclic ring system, each optionally substituted with from one to four substituents independently selected from W;

each W is independently C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_1-C_4 haloalkyl, C_2-C_4 haloalkenyl, C_2-C_4 haloalkynyl, C_3-C_6 halocycloalkyl, halogen, CN, NO_2, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, C_3-C_6 cycloalkylamino, (C_1-C_4 alkyl)(C_3-C_6 cycloalkyl)amino or C_3-C_6 trialkylsilyl;

each R^{12} is independently $R^{19}C(=E)-$; $R^{19}C(=E)L-$; $R^{19}LC(=E)-$; $(R^{19})LC(=E)L-$; $-O(Q=)P(OR^{19})_2$; $-SO_2LR^{18}$; or $R^{19}SO_2L-$;

each R^{13} is $B(OR^{17})_2$; NH_2; SH; thiocyanato; C_3-C_8 trialkylsilyloxy; C_1-C_4 alkyldisulfide; SF_5; $R^{19}C(=E)-$; $R^{19}C(=E)M-$; $R^{19}MC(=E)-$; $(R^{19})MC(=E)M-$; $-OP(=Q)(OR^{19})_2$; $-S(O)_2MR^{19}$; $R^{19}S(O)_2M-$;

each E is independently O, S, NR^{15}, NOR^{15}, $NN(R^{15})_2$, N-S=O, N-CN or N-NO_2;

each M is independently O, NR^{18} or S;

Q is O or S;

each R^{15} and each R^{19} is independently H; C_1-C_6 alkyl optionally substituted with one or more substituents selected from the group consisting of CN, NO_2, hydroxy, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, C_1-C_4 haloalkylthio, C_1-C_4 haloalkylsulfinyl, C_1-C_4 haloalkylsulfonyl, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, CO_2H, C_2-C_6 alkoxycarbonyl, C_2-C_6 alkylcarbonyl, C_3-C_6 trialkylsilyl, and a phenyl ring optionally substituted with one to three substituents independently selected from W; C_1-C_6 haloalkyl; C_3-C_6 cycloalkyl;

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or a phenyl ring optionally substituted with from one to three substituents
independently selected from W;

each R^{17} is independently H or C_1–C_4 alkyl; or

$B(OR^{17})_2$ can form a ring wherein the two oxygen atoms are linked by a chain of two
to three carbons optionally substituted with one or two substituents
independently selected from methyl or C_2–C_6 alkoxycarbonyl; and

each R^{18} is independently H, C_1–C_6 alkyl or C_1–C_6 haloalkyl.

Preferably, K is, together with the two contiguous linking carbon atoms, a fused
phenyl ring optionally substituted with from one to four substituents independently selected
from W or R^{13}.

The compounds of Formula 1 can be prepared by one or more of the following
methods and variations as described in Schemes 1–27. The definitions of J, K, L, M, R^4,
through R^9, R^v X, Y and n in the compounds of Formulae 2–76 below are as defined above.
Compounds of Formulae 1a, 2', and 2a–p, 5', 9a-b and 25a-c are various subsets of the
compounds of Formula 1, 2, 5, 9 and 25, respectively. Of note are compounds wherein K is
selected from the group consisting of optionally substituted thiophene, isoxazole, isothiazole,
pyrazole, pyridine and pyrimidine rings. Also of note are compounds wherein K is K-1, K-
14, K-15, K-18, K-23, K-28, K-29, K-30, K-31 and K-33. Of particular note are compounds
wherein K is K-28, K-31 and K-33. Also of particular note are compounds wherein K is an
optionally substituted fused phenyl ring (K-38).

As shown in Scheme 1, according to the method of this invention a fused oxazinone
of Formula 1 is prepared via coupling of a carboxylic acid of Formula 2 with an isatoic
anhydride of Formula 5 in the presence of a sulfonyl chloride 4 and a tertiary amine 3 in a
suitable solvent.

<u>Scheme 1</u>
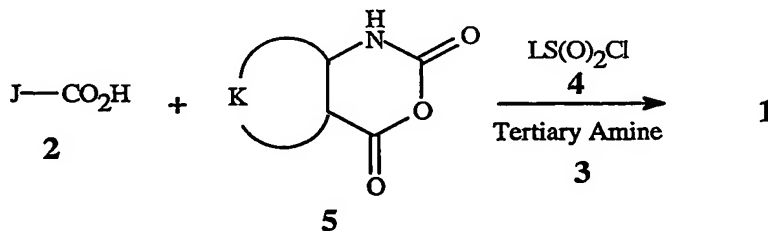
The reaction components can be added to the reaction vessel in various sequences or added
as mixtures. Suitable solvents include aromatic hydrocarbons such as chlorobenzene or
toluene, and preferred solvents include esters such as ethyl acetate or butyl acetate; ketones
such as acetone, 2-butanone, or 4-methyl-2-pentanone; ethers such as tetrahydrofuran (THF)
or dioxane; nitriles such as acetonitrile; and halocarbons such as dichloromethane or
chloroform. More preferred solvents include acetonitrile, ethyl acetate, acetone, THF and

dichloromethane.   Most preferred solvents are acetonitrile and acetone.   The reaction is typically conducted at temperatures ranging from –30 °C to +100 °C.   Preferred is the addition to the reaction vessel (charging) of all components at temperatures from –10 °C to +5 °C, with intervening periods of from 1 to 30 minutes (preferred are intervening periods of 5   from 5 to 15 minutes) between additions followed by warming the reaction mixture to from +20°C to +50°C for 0.5 to 24 hours (preferably 2 to 4 hours).   Charging of a component (for example, a reactant, a solvent, etc.) means adding the component during the step.   One of ordinary skill in the art will recognize that a component may be added (i.e. charged) in various ways, for example as a batch, intermittent or continuous feed depending on process 10   design.   The nominal mole ratio of the Formula 4 compound to the Formula 2 compound is typically from about 1.0 to 1.5, and preferably is from about 1.1 to 1.3.   Preferred Formula 4 compounds include methanesulfonyl chloride, propanesulfonyl chloride and benzenesulfonyl chloride. Methanesulfonyl chloride is more preferred for reasons of lower cost and/or less waste.   The nominal mole ratio of the Formula 3 compound charged to the Formula 2 15   compound charged is typically from about 2.0 to 4.0, and is preferably from about 2.8 to 3.4. The nominal mole ratio of the Formula 5 compound to the Formula 2 compound is typically from about 0.9 to 1.1, and is preferably about 1.0.   Preferred Formula 3 compounds include 2-picoline, 3-picoline, 2,6-lutidine, and pyridine.   The compounds of Formulae 2, 3, 4 and 5 can be combined in any order or as a mixture in solvent.

20   Preferred methods of this invention include the method wherein the carboxylic acid of Formula 2 is Formula 2', the isatoic anhydride of Formula 5 is Formula 5' and the product compound of Formula 1 is Formula 1a as shown in Scheme 2.

<center>Scheme 2</center>
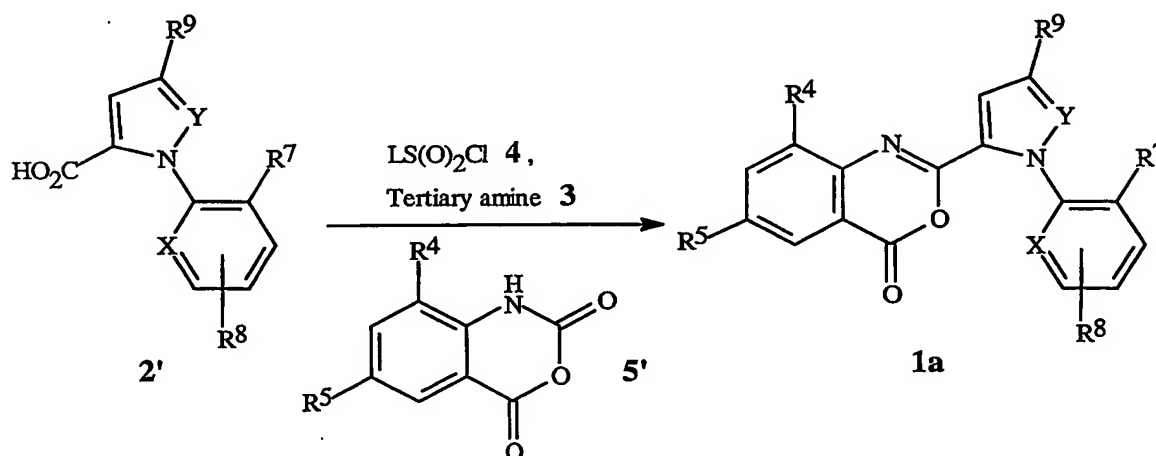
25   wherein

        X is N or CR^6;

        Y is N or CH;

        R^4 is C_1–C_4 alkyl or halogen;

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R^5 is H, C_1–C_4 alkyl, C_1–C_4 haloalkyl, CN or halogen;

R^6 and R^7 are independently H, C_1–C_4 alkyl, C_1–C_4 haloalkyl, halogen, CN or C_1–C_4 haloalkoxy;

R^8 is H, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, C_3–C_6 cycloalkyl, C_1–C_4 haloalkyl, C_2–C_4 haloalkenyl, C_2–C_4 haloalkynyl, C_3–C_6 halocycloalkyl, halogen, CN, NO_2, C_1–C_4 alkoxy, C_1–C_4 haloalkoxy, C_1–C_4 alkylthio, C_1–C_4 alkylsulfinyl, C_1–C_4 alkylsulfonyl, C_1–C_4 alkylamino, C_2–C_8 dialkylamino, C_3–C_6 cycloalkylamino, (C_1–C_4 alkyl)(C_3–C_6 cycloalkyl)amino, C_2–C_4 alkylcarbonyl, C_2–C_6 alkoxycarbonyl, C_2–C_6 alkylaminocarbonyl, C_3–C_8 dialkylaminocarbonyl or C_3–C_6 trialkylsilyl;

R^9 is CF_3, OCF_3, $OCHF_2$, OCH_2CF_3, $S(O)_pCF_3$, $S(O)_pCHF_2$ or halogen; and

p is 0, 1 or 2.

Compounds of Formula **1a** may be prepared in this way and used for preparing compounds of Formula **III**.

Isatoic anhydrides of Formula **5** can be made by a variety of known methods which are well documented in the chemical literature. For example, isatoic anhydrides are available from the corresponding anthranilic acids via cyclization involving reaction of the anthranilic acid with phosgene or a phosgene equivalent. For leading references to the methods see, Coppola, *Synthesis* **1980**, 505 and Fabis et al., *Tetrahedron*, **1998**, 10789.

The synthesis of the isatoic anhydrides of Formula **5'** can be achieved from isatins of Formula **7** as outlined in Scheme 3.

Scheme 3
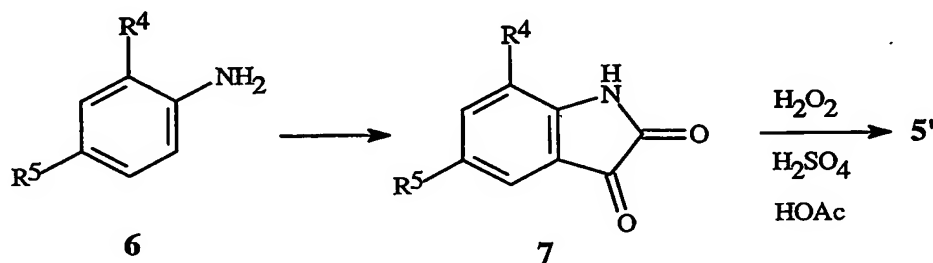
Isatins of Formula **7** are available from aniline derivatives of Formula **6** following literature procedures such as F. D. Popp, *Adv. Heterocycl. Chem.* **1975**, *18*, 1–58 and J. F. M. Da Silva et al., *Journal of the Brazilian Chemical Society* **2001**, *12*(3), 273–324. Oxidation of isatin **7** with hydrogen peroxide generally affords good yields of the corresponding isatoic anhydride **5'** (G. Reissenweber and D. Mangold, *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 222–223).

As shown in Scheme 4, isatoic anhydrides of Formula **5'** (compounds of Formula **5** wherein K is a fused phenyl ring with substituents R^4 and R^5) are typically available from the corresponding 2-nitrobenzoic acids (or esters) of Formula **9** via catalytic hydrogenation of the nitro group followed by reaction with phosgene or a phosgene equivalent. Typical

reduction procedures involve reduction with hydrogen in the presence of a metal catalyst such as palladium on carbon or platinum oxide in hydroxylic solvents such as ethanol and isopropanol. The reduction can also be conducted in the presence of zinc in acetic acid. These methods for reducing nitro groups are well documented in the chemical literature.
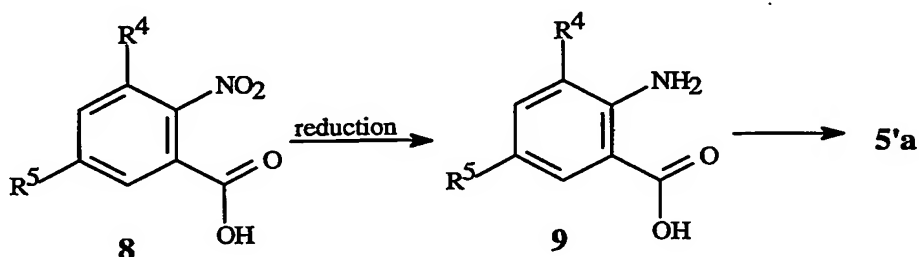
Scheme 4

As shown in Scheme 5, anthranilic acids containing an R^5 substituent of chloro, bromo or iodo can be prepared by direct halogenation of an anthranilic acid of Formula 9a with N-chlorosuccinimide (NCS), N-bromosuccinimide (NBS) or N-iodosuccinimide (NIS) respectively in solvents such as N,N-dimethylformamide (DMF) to produce the corresponding substituted acid of Formula 9b.

Scheme 5
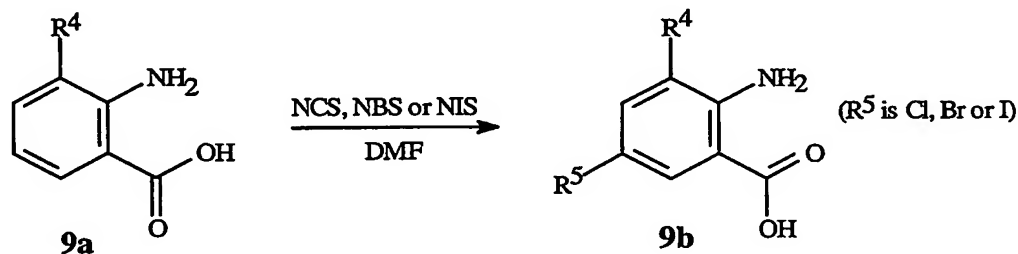
Benzoic acids of Formula 2 (wherein J is optionally substituted phenyl) are generally well known in the art as are procedures for their preparation.

Benzoic acids of Formula 2a may be prepared from the benzonitriles of Formula 10 by hydrolysis (Scheme 6). The conditions used may involve the use of a base such as an alkaline metal hydroxide or alkoxide (e.g., potassium or sodium hydroxide) in a solvent such as water, ethanol or ethylene glycol (see e.g., *J. Chem. Soc.* 1948, 1025). Alternatively, the hydrolysis may be carried out using an acid such as sulfuric acid or phosphoric acid in a suitable solvent such as water (see e.g., *Org. Synth.* 1955, Coll vol. *3*, 557). The choice of the conditions is contingent on the stability of any optional substituents present on the aromatic ring to the reaction conditions, and elevated temperatures are usually employed to achieve this transformation.

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Scheme 6

10   Hydrolysis →   **2a**
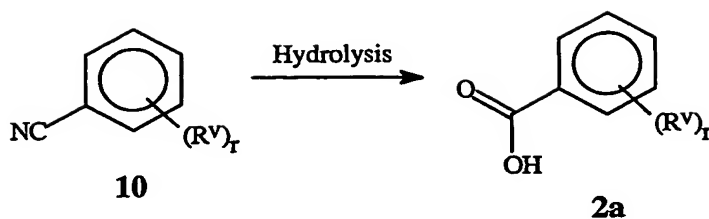
Nitriles of Formula **10** may be prepared from anilines of Formula **11** by the classical sequence involving diazotization and treatment of the intermediate diazonium salt with a copper cyanide salt (see e.g., *J. Amer. Chem. Soc.* **1902**, *24*, 1035).

Scheme 7

11   1) Diazotization / 2) Copper cyanide →   **10**
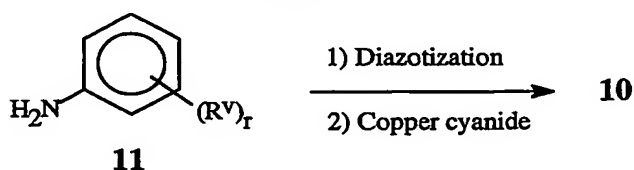
5   Certain heterocyclic acids of Formula **2**, wherein J is an optionally substituted heterocycle, can be prepared by procedures outlined in Schemes 8 through 27. Both general and specific references to a wide variety of heterocyclic acids including thiophenes, furans, pyridines, pyrimidines, triazoles, imidazoles, pyrazoles, thiazoles, oxazoles, isothiazoles, thiadiazoles, oxadiazoles, triazines, pyrazines, pyridazines, and isoxazoles can be found in

10   the following compendia: *Rodd's Chemistry of Chemistry of Carbon Compounds*, Vol. IVa to IVl., S. Coffey editor, Elsevier Scientific Publishing, New York, **1973**; *Comprehensive Heterocyclic Chemistry*, Vol. *1–7*, A. R. Katritzky and C. W. Rees editors, Pergamon Press, New York, **1984**; *Comprehensive Heterocyclic Chemistry II*, Vol. *1–9*, A. R. Katritzky, C. W. Rees, and E. F. Scriven editors, Pergamon Press, New York, **1996**; and the series, *The*

15   *Chemistry of Heterocyclic Compounds*, E. C. Taylor, editor, Wiley, New York. Noteworthy heterocyclic acids suitable for use in this invention include pyridine acids, pyrimidine acids, pyrazole acids and pyrrole acids. Procedures for the synthesis of representative examples of each are detailed in Schemes 8 through 27. A variety of heterocyclic acids and general methods for their synthesis may be found in PCT Patent Publication WO 98/57397.

20   The synthesis of representative pyridine acids of Formula **2b** is depicted in Scheme 8. This procedure involves the known synthesis of pyridines from β-ketoesters (Formula **16**) and 4-aminobutenones (Formula **15**). Substituent groups R^a and R^b include, for example, alkyl, haloalkyl, and optionally substituted aromatic and heteroaromatic rings.

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Scheme 8
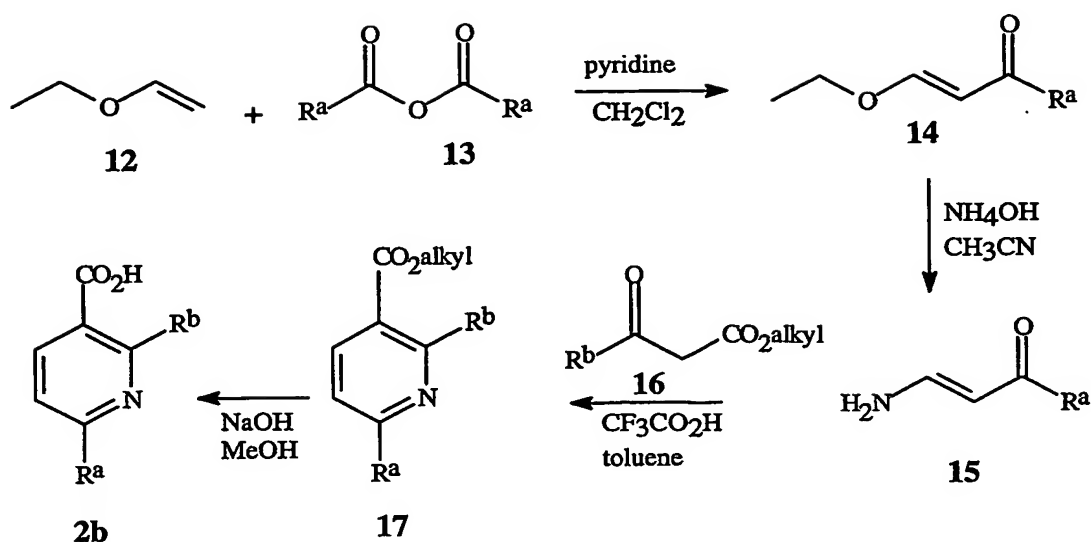
The synthesis of representative pyrimidine acids (Formula 2c) is depicted in Scheme 9. This procedure involves the known synthesis of pyrimidines from vinylidene-β-ketoesters (Formula 16) and amidines (Formula 20). Substituent groups R^a and R^b include, for example, alkyl, haloalkyl, and optionally substituted aromatic and heteroaromatic rings.

Scheme 9
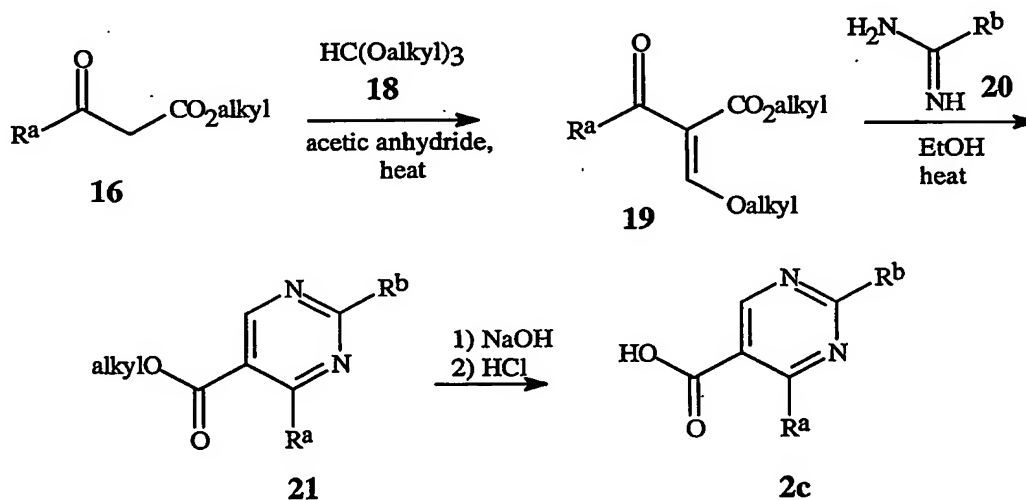
Syntheses of representative pyrazole acids (Formula 2d–2g) are depicted in Schemes 10 through 13. The synthesis of 2d in Scheme 10 involves as the key step introduction of the R^a substituent via alkylation of the pyrazole. The alkylating agent R^a-Lg (wherein Lg is a leaving group such as Cl, Br, I, sulfonates such as p-toluenesulfonate, methanesulfonate or trifluoromethanesulfonate, or sulfates such as -SO_2OR^a) includes R^a groups such as C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_3–C_6 cycloalkyl, C_1–C_6 haloalkyl, C_2–C_6

haloalkenyl, C_2–C_6 haloalkynyl, C_3–C_6 halocycloalkyl, C_2–C_6 alkylcarbonyl, C_2–C_6 alkoxycarbonyl, C_3–C_8 dialkylamino-carbonyl, C_3–C_6 trialkylsilyl; or phenyl, benzyl, benzoyl, 5- or 6-membered heteroaromatic rings or aromatic 8-, 9- or 10-membered fused heterobicyclic ring systems, each ring or ring system optionally substituted. (As referred to herein, the terms "alkylation" and "alkylating agent" are not limited to R^a being an alkyl group.) Oxidation of the methyl group affords the pyrazole carboxylic acid. Some notable R^b groups include haloalkyl.

<u>Scheme 10</u>

22   Lg is a leaving group   24   2d
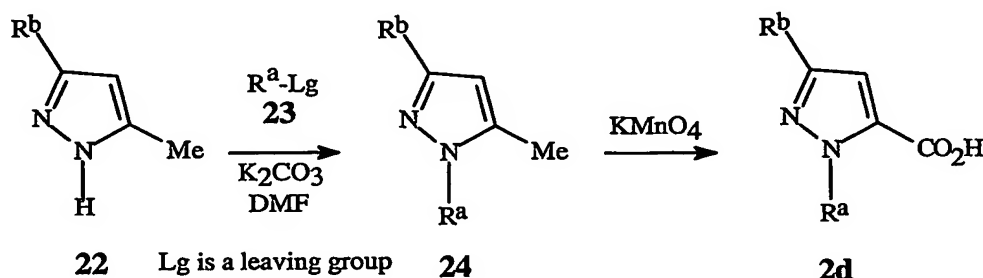
Alkylation of pyrazoles using potassium carbonate and N,N-dimethylformamide (DMF) are described by T. Kitazaki et al., *Chem. Pharm. Bull.* **2000**, *48*(12), 1935–1946. One skilled in the art recognizes that a variety of bases and solvents can be used for alkylation of pyrazoles. For example, C. T. Alabaster et al., *J. Med. Chem.* **1989**, *32*, 575–583 discloses use of sodium carbonate in DMF, X. Wang et al., *Org. Lett.* **2000**, *2*(20), 3107–3109 discloses use of potassium *tert*-butoxide in methyl sulfoxide, and European Patent Application Publication EP-1081146-A1 describes the use of methyl sulfoxide and sodium or potassium hydroxide in the presence of a phase transfer catalyst or cesium carbonate. One skilled in the art also recognizes that a variety of alternative synthetic methods are applicable to the coupling of a pyrazole of Formula 22 to form a pyrazole of Formula 24 (or coupling of a pyrazole of Formula 25 below to form a pyrazole of Formula 26 below). These methods include, for example, condensation with aryl iodides in the presence of copper(I) iodide and *trans*-cyclohexanediamine as reported by A. Klapars, J. C. Antilla, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729, and condensation with aryl boronic acids in the presence of copper(II) acetate and pyridine as reported by P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan and A. Combs, *Tetrahedron Lett.* **1998**, *39*, 2941–2944.

Some pyrazole acids of Formula 2d may be prepared via metallation and carboxylation of pyrazoles of Formula 26 as the key step (Scheme 11). This reaction is typically conducted by treating compounds of Formula 25 with lithium diisopropylamide (LDA) to form an anion and then contacting the anion with carbon dioxide. The R^a group is

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introduced in a manner similar to that of Scheme 10, i.e. via alkylation with an R^a alkylating agent. Representative R^b groups include, for example, cyano and haloalkyl.

<u>Scheme 11</u>
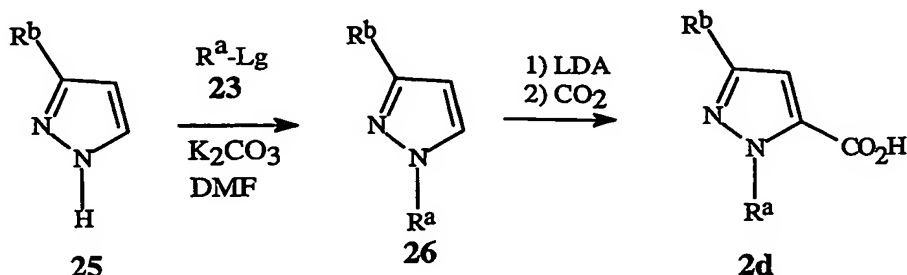
5   This procedure is particularly useful for preparing 1-(2-pyridinyl)pyrazolecarboxylic acids of Formula **2e**, wherein R^a is a substituted 2-pyridinyl ring, as shown in Scheme 12. Reaction of a pyrazole of Formula **27** with a 2-halopyridine of Formula **28** affords good yields of the 1-pyridinylpyrazole of Formula **29** with good specificity for the desired regiochemistry. Metallation of **29** with LDA followed by quenching of the lithium salt with 10   carbon dioxide affords the 1-(2-pyridinyl)pyrazolecarboxylic acid of Formula **2e**. For a leading reference to this method see, WO 03/015519.

<u>Scheme 12</u>
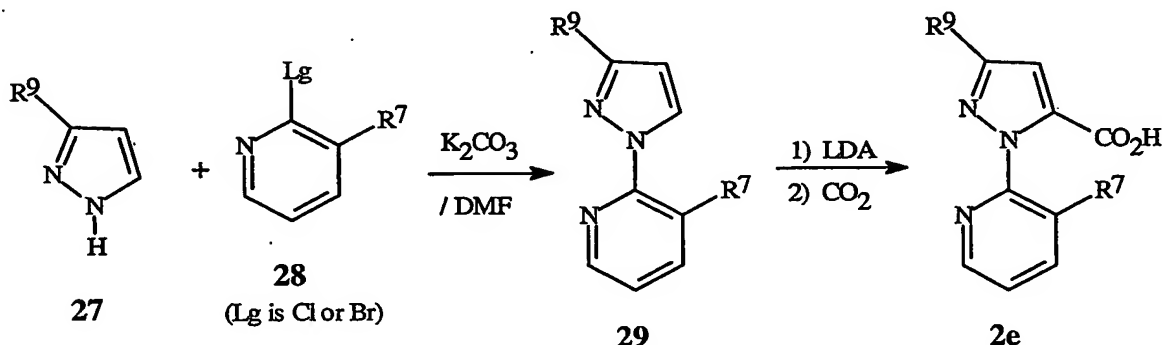
wherein R^7 is H, C_1–C_4 alkyl, C_1–C_4 haloalkyl, halogen, CN or C_1–C_4 haloalkoxy; and
15   R^9 is CF_3, OCF_3, $OCHF_2$, OCH_2CF_3, $S(O)_pCF_3$, $S(O)_pCHF_2$ or halogen.

Other pyrazoles of Formula **2d** can be prepared via reaction of hydrazine of Formula **31** with a pyruvate of Formula **30** to yield pyrazole esters of Formula **32** (Scheme 13). Hydrolysis of the ester affords the pyrazole acids **2d**. This procedure is particularly useful for the preparation of compounds wherein R^a is optionally substituted 20   phenyl and R^b is haloalkyl.

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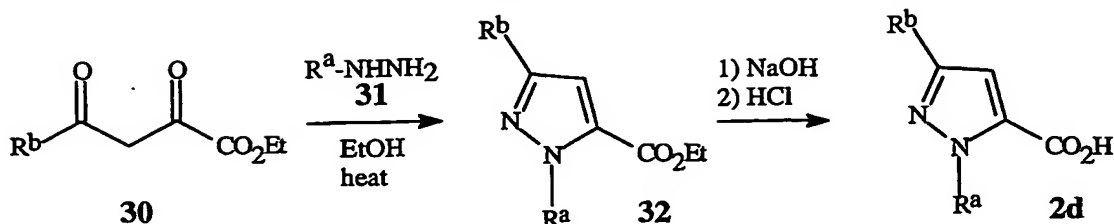
Scheme 13

Pyrazole acids of Formula **2d** can also be prepared via 3+2 cycloaddition of an appropriately substituted iminohalide of Formula **33** with either substituted propiolates of Formula **34** or acrylates of Formula **35** (Scheme 14). Cycloaddition with acrylates requires additional oxidation of the intermediate pyrazoline to the pyrazole. Hydrolysis of the ester of Formula **36** affords the pyrazole acids **2d**. Preferred iminohalides for this reaction include the trifluoromethyl iminochloride (**37**) and the iminodibromide (**38**). Compounds such as **37** are known (*J. Heterocycl. Chem.* **1985**, *22*(2), 565–8). Compounds such as **38** are available by known methods (*Tetrahedron Letters* **1999**, *40*, 2605). These procedures are particularly useful for the preparation of compounds where R^a is optionally substituted phenyl and R^b is haloalkyl or bromo.

Scheme 14

Hal is halogen
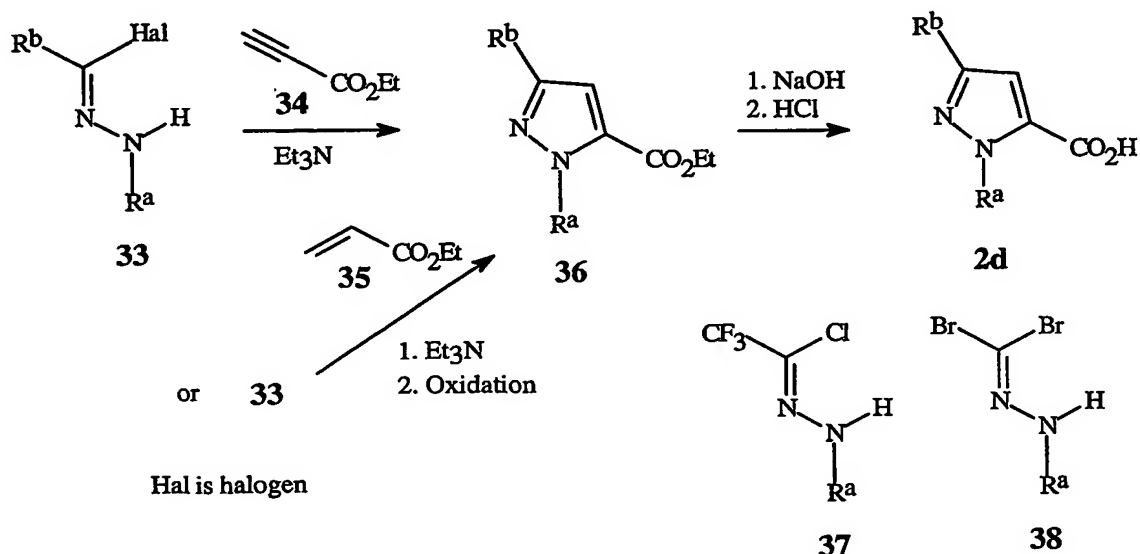
The starting pyrazoles of Formula **25** are known compounds or can be prepared according to known methods. The pyrazole of Formula **25a** (the compound of Formula **25** wherein R^b is CF_3) can be prepared by literature procedures (*J. Fluorine Chem.* **1991**, *53*(1), 61–70). The pyrazoles of Formula **25b** (compounds of Formula **25** wherein R^b is Cl or Br) can be prepared by literature procedures (*Chem. Ber.* **1966**, *99*(10), 3350–7). A useful alternative method for the preparation of a compound of Formula **25b** is depicted in

Scheme 15. Metallation of the sulfamoyl pyrazole of Formula **39** with *n*-butyllithium followed by direct halogenation of the anion with either hexachloroethane (for R^b being Cl) or 1,2-dibromotetrachloroethane (for R^b being Br) affords the halogenated derivatives of Formula **40**. Removal of the sulfamoyl group with trifluoroacetic acid (TFA) at room temperature proceeds cleanly and in good yield to afford the pyrazoles of Formula **25c**. One skilled in the art will recognize that Formula **25c** is a tautomer of Formula **25b**.

<p align="center">Scheme 15</p>
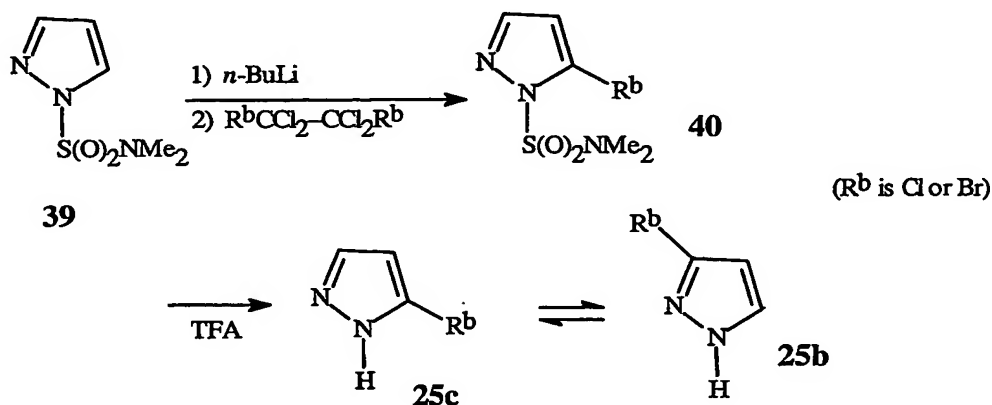
Pyrazolecarboxylic acids of Formula **2f** wherein R^{10} is CF_3 can be prepared by the method outlined in Scheme 16.

<p align="center">Scheme 16</p>
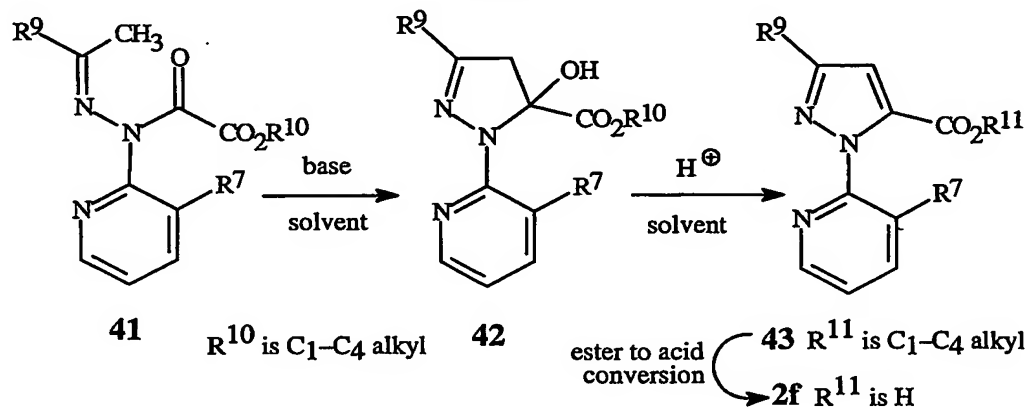
Reaction of a compound of Formula **41** wherein R^{10} is C_1–C_4 alkyl with a suitable base in a suitable organic solvent affords the cyclized product of Formula **42** after neutralization with an acid such as acetic acid. The suitable base can be, for example but not limitation, sodium hydride, potassium *t*-butoxide, dimsyl sodium ($CH_3S(O)CH_2^-Na^+$), alkali metal (such as lithium, sodium or potassium) carbonates or hydroxides, tetraalkyl (such as methyl, ethyl or butyl)ammonium fluorides or hydroxides, or 2-*tert*-butylimino-2-diethyl-amino-1,3-dimethyl-perhydro-1,3,2-diazaphosphonine. The suitable organic solvent can be, for example but not limitation, acetone, acetonitrile, tetrahydrofuran, dichloromethane,

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dimethylsulfoxide, or *N,N*-dimethylformamide. The cyclization reaction is usually conducted in a temperature range from about 0 to 120 °C. The effects of solvent, base, temperature and addition time are all interdependent, and choice of reaction conditions is important to minimize the formation of byproducts. A preferred base is tetrabutyl-
5   ammonium fluoride.

Dehydration of the compound of Formula 42 to give the compound of Formula 43, followed by converting the carboxylic ester function to carboxylic acid, affords the compound of Formula 2f. The dehydration is effected by treatment with a catalytic amount of a suitable acid. This catalytic acid can be, for example but not limitation, sulfuric acid.
10   The reaction is generally conducted using an organic solvent. As one skilled in the art will realize, dehydration reactions may be conducted in a wide variety of solvents in a temperature range generally between about 0 and 200 °C, more preferably between about 0 and 100 °C. For the dehydration in the method of Scheme 16, a solvent comprising acetic acid and temperatures of about 65 °C are preferred. Carboxylic ester compounds can be
15   converted to carboxylic acid compounds by numerous methods including nucleophilic cleavage under anhydrous conditions or hydrolytic methods involving the use of either acids or bases (see T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd ed., John Wiley & Sons, Inc., New York, 1991, pp. 224–269 for a review of methods). For the method of Scheme 16, base-catalyzed hydrolytic methods are preferred. Suitable bases
20   include alkali metal (such as lithium, sodium or potassium) hydroxides. For example, the ester can be dissolved in a mixture of water and an alcohol such as ethanol. Upon treatment with sodium hydroxide or potassium hydroxide, the ester is saponified to provide the sodium or potassium salt of the carboxylic acid. Acidification with a strong acid, such as hydrochloric acid or sulfuric acid, yields the carboxylic acid of Formula 2f. The carboxylic
25   acid can be isolated by methods known to those skilled in the art, including crystallization, extraction and distillation.

Compounds of Formula 41 can be prepared by the method outlined in Scheme 17.

<u>Scheme 17</u>

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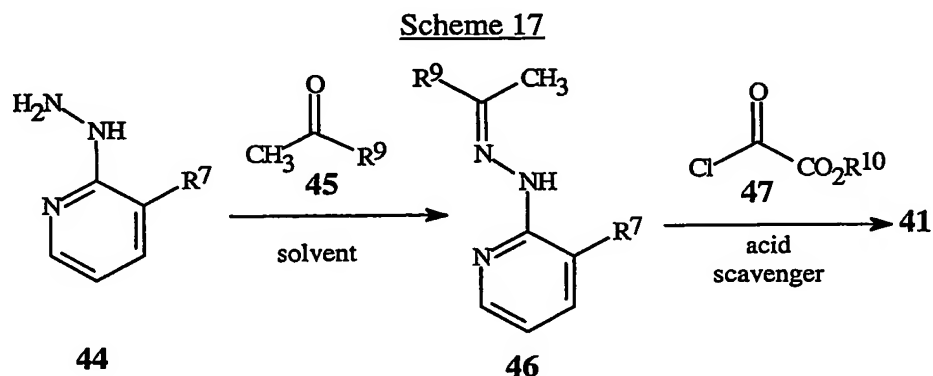
wherein R^9 is CF_3 and R^{10} is C_1–C_4 alkyl.

Treatment of a hydrazine compound of Formula **44** with a ketone of Formula **45** in a solvent such as water, methanol or acetic acid gives the hydrazone of Formula **46**. One skilled in the art will recognize that this reaction may require catalysis by an optional acid and may also require elevated temperatures depending on the molecular substitution pattern of the
5   hydrazone of Formula **46**. Reaction of the hydrazone of Formula **46** with the compound of Formula **47** in a suitable organic solvent such as, for example but not limitation, dichloromethane or tetrahydrofuran in the presence of an acid scavenger such as triethylamine provides the compound of Formula **41**. The reaction is usually conducted at a temperature between about 0 and 100 °C. Hydrazine compounds of Formula **44** can be
10   prepared by standard methods, such as by contacting the corresponding halo compound of Formula **28** (Scheme 12) with hydrazine.

Pyrazolecarboxylic acids of Formula **2g** wherein R^9 is halogen such as Cl or Br can be prepared by the method outlined in Scheme 18.

<u>Scheme 18</u>

49 R^{11} is C_1-C_4 alkyl

2g R^{11} is H

ester to acid conversion
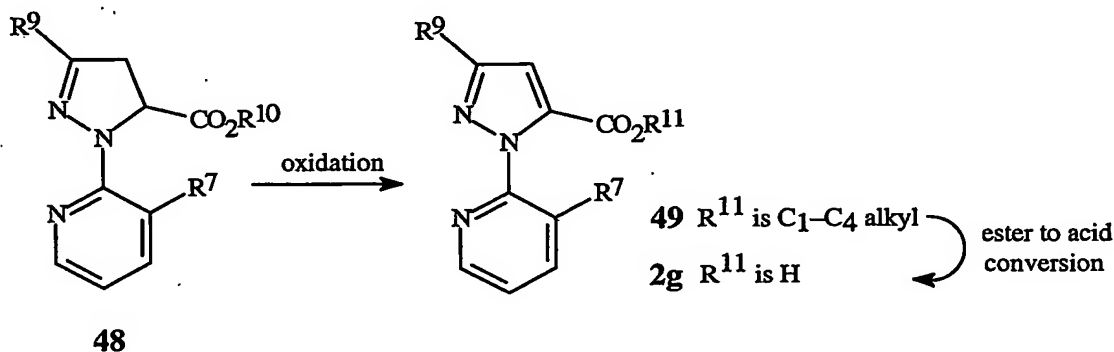
wherein R^{10} is C_1-C_4 alkyl.

Oxidation of the compound of Formula **48** optionally in the presence of acid to give the
15   compound of Formula **49** followed by conversion of the carboxylic ester function to the carboxylic acid provides the compound of Formula **2g**. The oxidizing agent can be hydrogen peroxide, organic peroxides, potassium persulfate, sodium persulfate, ammonium persulfate, potassium monopersulfate (e.g., Oxone®) or potassium permanganate. To obtain complete conversion, at least one equivalent of oxidizing agent versus the compound of
20   Formula **48** should be used, preferably between about one to two equivalents. This oxidation is typically carried out in the presence of a solvent. The solvent can be an ether, such as tetrahydrofuran, *p*-dioxane and the like, an organic ester, such as ethyl acetate, dimethyl carbonate and the like, or a polar aprotic organic such as *N,N*-dimethylformamide, acetonitrile and the like. Acids suitable for use in the oxidation step include inorganic acids,
25   such as sulfuric acid, phosphoric acid and the like, and organic acids, such as acetic acid, benzoic acid and the like. The acid, when used, should be used in greater than 0.1 equivalents versus the compound of Formula **48**. To obtain complete conversion, one to

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five equivalents of acid can be used. The preferred oxidant is potassium persulfate, and the oxidation is preferably carried out in the presence of sulfuric acid. The reaction can be carried out by mixing the compound of Formula **48** in the desired solvent and, if used, the acid. The oxidant can then be added at a convenient rate. The reaction temperature is typically varied from as low as about 0 °C up to the boiling point of the solvent in order to obtain a reasonable reaction time to complete the reaction, preferably less than 8 hours. The desired product, a compound of Formula **49**, can be isolated by methods known to those skilled in the art, including crystallization, extraction and distillation. Methods suitable for converting the ester of Formula **49** to the carboxylic acid of Formula **2g** are already described for Scheme 16.

Compounds of Formula **48** wherein R^9 is halogen such as Cl or Br can be prepared from corresponding compounds of Formula **50** as shown in Scheme 19.

Scheme 19
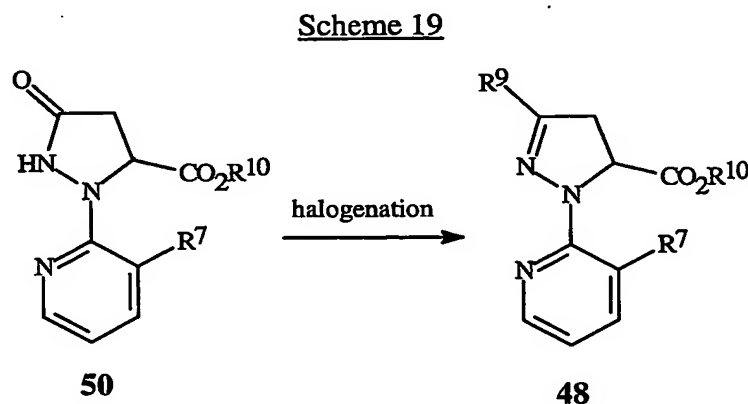
wherein R^{10} is C_1–C_4 alkyl.

Treatment of a compound of Formula **50** with a halogenating reagent, usually in the presence of a solvent, affords the corresponding halo compound of Formula **48** (R^9 is halogen). Halogenating reagents that can be used include phosphorus oxyhalides, phosphorus trihalides, phosphorus pentahalides, thionyl chloride, dihalotrialkylphophoranes, dihalotriphenylphosphoranes, oxalyl chloride and phosgene. Preferred are phosphorus oxyhalides and phosphorus pentahalides. To obtain complete conversion, at least 0.33 equivalents of phosphorus oxyhalide versus the compound of Formula **50** should be used (i.e. the mole ratio of phosphorus oxyhalide to the compound of Formula **50** is 0.33), preferably between about 0.33 and 1.2 equivalents. To obtain complete conversion, at least 0.20 equivalents of phosphorus pentahalide versus the compound of Formula **50** should be used, preferably between about 0.20 and 1.0 equivalents. Compounds of Formula **50** wherein R^{10} is C_1–C_4 alkyl are preferred for this reaction. Typical solvents for this halogenation include halogenated alkanes, such as dichloromethane, chloroform, chlorobutane and the like, aromatic solvents, such as benzene, xylene, chlorobenzene and the like, ethers, such as tetrahydrofuran, *p*-dioxane, diethyl ether, and the like, and polar aprotic

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solvents such as acetonitrile, *N,N*-dimethylformamide, and the like. Optionally, an organic base, such as triethylamine, pyridine, *N,N*-dimethylaniline or the like, can be added. Addition of a catalyst, such as *N,N*-dimethylformamide, is also an option. Preferred is the process in which the solvent is acetonitrile and a base is absent. Typically, neither a base nor

5   a catalyst is required when acetonitrile solvent is used. The preferred process is conducted by mixing the compound of Formula **50** in acetonitrile. The halogenating reagent is then added over a convenient time, and the mixture is then held at the desired temperature until the reaction is complete. The reaction temperature is typically between 20 °C and the boiling point of acetonitrile, and the reaction time is typically less than 2 hours. The reaction

10 mass is then neutralized with an inorganic base, such as sodium bicarbonate, sodium hydroxide and the like, or an organic base, such as sodium acetate. The desired product, a compound of Formula **48**, can be isolated by methods known to those skilled in the art, including crystallization, extraction and distillation.

    Alternatively, compounds of Formula **48** wherein R^9 is halogen such as Br or Cl can

15 be prepared by treating the corresponding compounds of Formula **48** wherein R^9 is a different halogen (e.g., Cl for making Formula **48** wherein R^9 is Br) or a sulfonate group such as methanesulfonate, benzenesulfonate or *p*-toluenesulfonate with hydrogen bromide or hydrogen chloride, respectively. By this method the R^9 halogen or sulfonate substituent on the Formula **48** starting compound is replaced with Br or Cl from hydrogen bromide or

20 hydrogen chloride, respectively. The reaction is conducted in a suitable solvent such as dibromomethane, dichloromethane, acetic acid, ethyl acetate or acetonitrile. The reaction can be conducted at or near atmospheric pressure or above atmospheric pressure in a pressure vessel. The hydrogen halide starting material can be added in the form of a gas to the reaction mixture containing the Formula **48** starting compound and solvent. When R^9 in

25 the starting compound of Formula **48** is a halogen such as Cl, the reaction is preferably conducted in such a way that the hydrogen halide generated from the reaction is removed by sparging or other suitable means. Alternatively, the hydrogen halide starting material can be first dissolved in an inert solvent in which it is highly soluble (such as acetic acid) before contacting with the starting compound of Formula **48** either neat or in solution. Also when

30 R^9 in the starting compound of Formula **48** is a halogen such as Cl, substantially more than one equivalent of hydrogen halide starting material (e.g., 4 to 10 equivalents) is typically needed depending upon the level of conversion desired. One equivalent of hydrogen halide starting material can provide high conversion when R^9 in the starting compound of Formula **48** is a sulfonate group, but when the starting compound of Formula **48** comprises at least

35 one basic function (e.g., a nitrogen-containing heterocycle), more than one equivalent of hydrogen halide starting material is typically needed. The reaction can be conducted between about 0 and 100 °C, most conveniently near ambient temperature (e.g., about 10 to 40 °C), and more preferably between about 20 and 30 °C. Addition of a Lewis acid catalyst

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(such as aluminum tribromide for preparing Formula **48** wherein R^9 is Br) can facilitate the reaction. The product of Formula **48** is isolated by the usual methods known to those skilled in the art, including extraction, distillation and crystallization.

Starting compounds of Formula **48** wherein R^9 is Cl or Br can be prepared from corresponding compounds of Formula **50** as already described. Starting compounds of Formula **48** wherein R^9 is a sulfonate group can likewise be prepared from corresponding compounds of Formula **50** by standard methods such as treatment with a sulfonyl chloride (e.g., methanesulfonyl chloride, benzenesulfonyl chloride or p-toluenesulfonyl chloride) and base such as a tertiary amine (e.g., triethylamine) in a suitable solvent such as dichloromethane.

Pyrazolecarboxylic acids of Formula **2h** wherein R^9 is OCH_2CF_3 or Formula **2i** wherein R^9 is $OCHF_2$ can be prepared by the method outlined in Scheme 20. In this method, instead of being halogenated as shown in Scheme 19, the compound of Formula **50** is oxidized to the compound of Formula **51**. The reaction conditions for this oxidation are as already described for the conversion of the compound of Formula **48** to the compound of Formula **49** in Scheme 18.

The compound of Formula **51** is then alkylated to form the compound of Formula **54** (R^9 is OCH_2CF_3) by contact with an alkylating agent CF_3CH_2Lg (**52**) in the presence of a base. In the alkylating agent **52**, Lg is a nucleophilic reaction leaving group such as halogen (e.g., Br, I), $OS(O)_2CH_3$ (methanesulfonate), $OS(O)_2CF_3$, $OS(O)_2Ph$-p-CH_3 (p-toluene-sulfonate), and the like; methanesulfonate works well. The reaction is conducted in the presence of at least one equivalent of a base. Suitable bases include inorganic bases, such as alkali metal (such as lithium, sodium or potassium) carbonates and hydroxides, and organic bases, such as triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene. The reaction is generally conducted in a solvent, which can comprise alcohols, such as methanol and ethanol, halogenated alkanes, such as dichloromethane, aromatic solvents, such as benzene, toluene and chlorobenzene, ethers, such as tetrahydrofuran, and polar aprotic solvents, such as acetonitrile, N,N-dimethylformamide, and the like. Alcohols and polar aprotic solvents are preferred for use with inorganic bases. Potassium carbonate as base and acetonitrile as solvent are preferred. The reaction is typically conducted between about 0 and 150 °C, and more typically between ambient temperature and 100 °C.

·34

Scheme 20
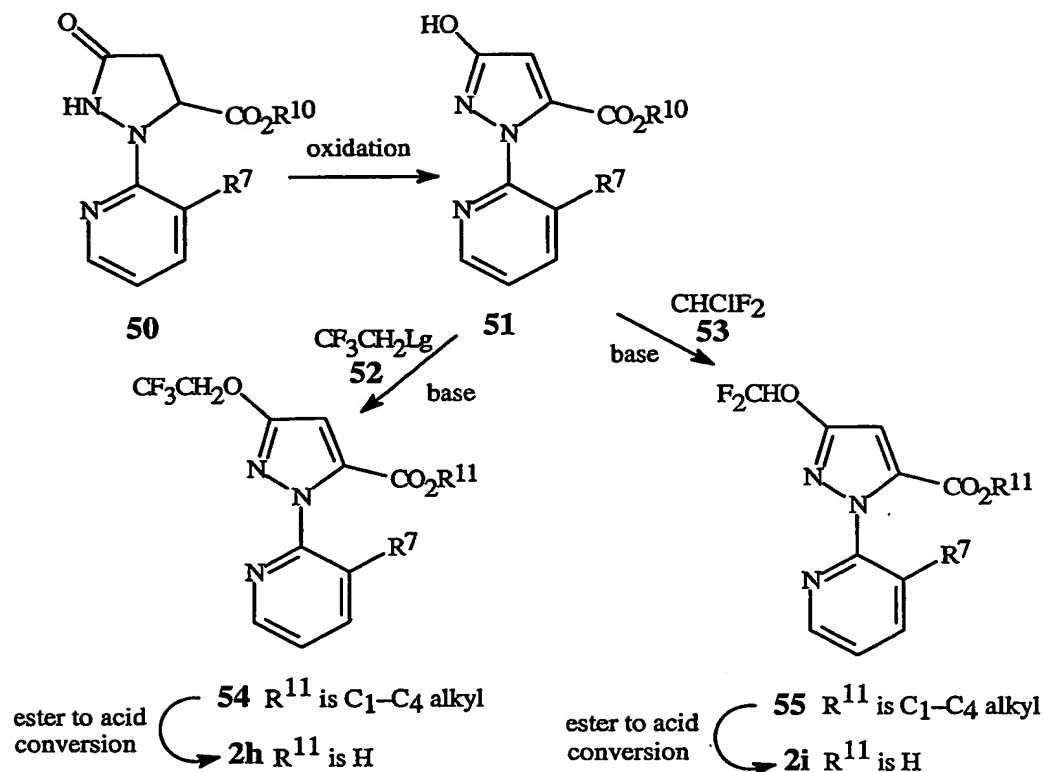
wherein R^{10} is C_1–C_4 alkyl, and Lg is a leaving group.

The compound of Formula **51** can also be alkylated to form the compound of Formula **55** (R^9 is $OCHF_2$) by contact with difluorocarbene, prepared from $CHClF_2$ (**53**) in the presence of a base. The reaction is generally conducted in a solvent, which can comprise ethers, such as tetrahydrofuran or dioxane, and polar aprotic solvents, such as acetonitrile, N,N-dimethylformamide, and the like. The base can be selected from inorganic bases such as potassium carbonate, sodium hydroxide or sodium hydride. Preferably the reaction is conducted using potassium carbonate with N,N-dimethylformamide as the solvent. The product of Formula **54** or **55** can be isolated by conventional techniques such as extraction. The esters can then be converted to the carboxylic acids of Formula **2h** or **2i** by the methods already described for the conversion of Formula **43** to Formula **2f** in Scheme 16.

Compounds of Formula **50** can be prepared from compounds of Formula **44** (see Scheme 17) as outlined in Scheme 21.

35

Scheme 21
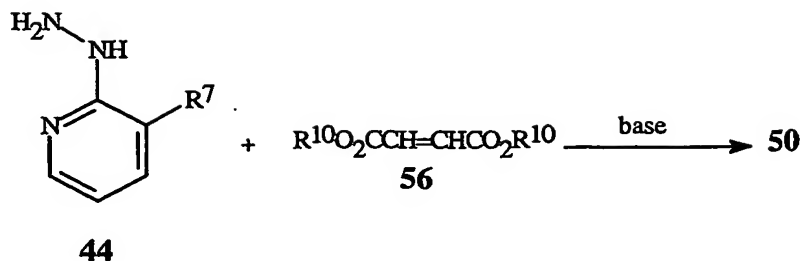
wherein R^{10} is C_1–C_4 alkyl.

In this method, a hydrazine compound of Formula **44** is contacted with a compound of
Formula **56** (a fumarate ester or maleate ester or a mixture thereof may be used) in the
presence of a base and a solvent. The base is typically a metal alkoxide salt, such as sodium
methoxide, potassium methoxide, sodium ethoxide, potassium ethoxide, potassium
tert-butoxide, lithium *tert*-butoxide, and the like. Greater than 0.5 equivalents of base versus
the compound of Formula **56** should be used, preferably between 0.9 and 1.3 equivalents.
Greater than 1.0 equivalents of the compound of Formula **44** should be used, preferably
between 1.0 to 1.3 equivalents. Polar protic and polar aprotic organic solvents can be used,
such as alcohols, acetonitrile, tetrahydrofuran, *N,N*-dimethylformamide, dimethyl sulfoxide
and the like. Preferred solvents are alcohols such as methanol and ethanol. It is especially
preferred that the alcohol be the same as that making up the fumarate or maleate ester and
the alkoxide base. The reaction is typically conducted by mixing the compound of
Formula **56** and the base in the solvent. The mixture can be heated or cooled to a desired
temperature and the compound of Formula **44** added over a period of time. Typically
reaction temperatures are between 0 °C and the boiling point of the solvent used. The
reaction may be conducted under greater than atmospheric pressure in order to increase the
boiling point of the solvent. Temperatures between about 30 and 90 °C are typically
preferred. The addition time can be as quick as heat transfer allows. Typical addition times
are between 1 minute and 2 hours. Optimum reaction temperature and addition time vary
depending upon the identities of the compounds of Formula **44** and Formula **56**. After
addition, the reaction mixture can be held for a time at the reaction temperature. Depending
upon the reaction temperature, the required hold time may be from 0 to 2 hours. Typical
hold times are 10 to 60 minutes. The reaction mass then can be acidified by adding an
organic acid, such as acetic acid and the like, or an inorganic acid, such as hydrochloric acid,
sulfuric acid and the like. Depending on the reaction conditions and the means of isolation,
the -CO_2R^{10} function on the compound of Formula **50** may be hydrolyzed to -CO_2H; for
example, the presence of water in the reaction mixture can promote such hydrolysis. If the
carboxylic acid (-CO_2H) is formed, it can be converted back to -CO_2R^{10} wherein R^{10} is
C_1–C_4 alkyl using esterification methods well known in the art. The desired product, a

compound of Formula **50**, can be isolated by methods known to those skilled in the art, such as crystallization, extraction or distillation.

The synthesis of representative pyrazole acids of Formula **2j** is depicted in Scheme 22. Reaction of a dimethylaminoylidene ketoester of Formula **58** with substituted hydrazines of

5   Formula **31** affords the pyrazoles of Formula **59**. Substituent groups R^a and R^b include, for example, alkyl, haloalkyl, and optionally substituted aromatic and heteroaromatic rings. Notable R^a substituents include alkyl and haloalkyl, with 2,2,2-trifluoroethyl especially noteworthy, and R^b substituents include optionally substituted phenyl or pyridine. The esters of Formula **59** are converted to the acids of Formula **2j** by standard hydrolysis

10   methods.
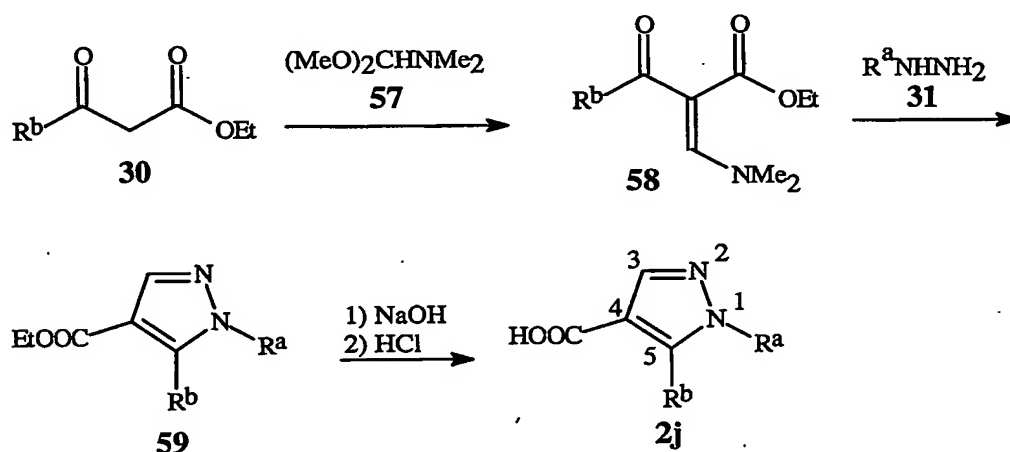
<u>Scheme 22</u>

The synthesis of pyrazole acids of Formula **2k**, a subset of the pyrazole acids of Formula **2j** wherein R^b is a substituted 2-pyridyl moiety attached to the 5-position of the

15   pyrazole ring, is depicted in Scheme 23. This synthesis is conducted according to the general synthesis described in Scheme 22. Notable R^c substituents include hydrogen and halogen.

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Scheme 23
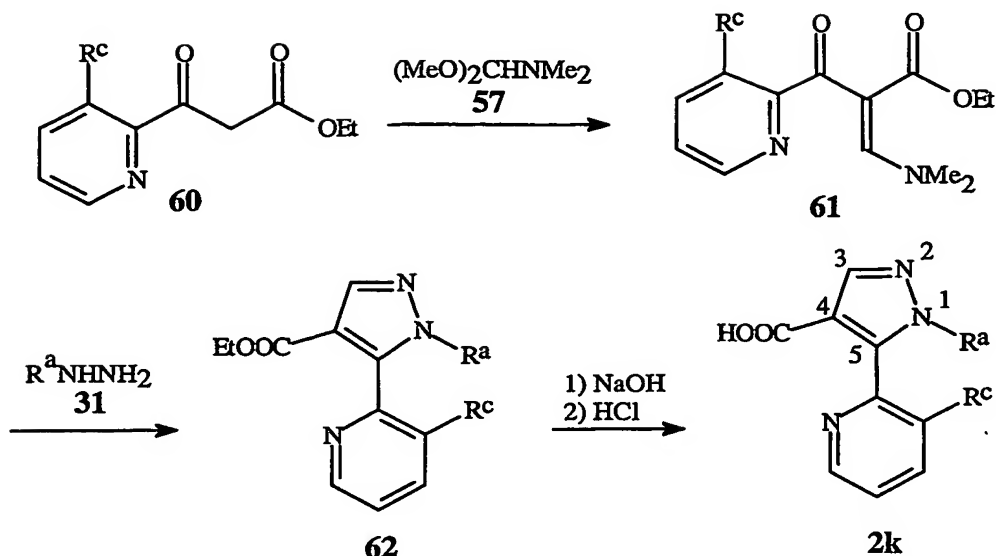
The synthesis of representative pyrazole acids of Formula **2m**, as well as an alternative synthesis of Formula **2j**, is depicted in Scheme 24. Reaction of the dimethylaminoylidene ketoester of Formula **58** with hydrazine affords the pyrazole of Formula **63**. Reaction of the pyrazole **63** with alkylating agents of Formula **23** (R^a-Lg wherein Lg is a leaving group such as halogen (e.g., Br, I), $OS(O)_2CH_3$ (methanesulfonate), $OS(O)_2CF_3$, $OS(O)_2Ph$-p-CH_3 (p-toluenesulfonate), and the like) affords a mixture of pyrazoles of Formulae **64** and **65**. This mixture of pyrazole isomers is readily separated by chromatographic methods and converted to the corresponding acids **2m** and **2j**. Substituent groups R^a and R^b include, for example, alkyl, haloalkyl, and optionally substituted aromatic and heteroaromatic rings. Noteworthy R^a substituents include alkyl and haloalkyl groups and R^b substituents include optionally substituted phenyl or pyridine.

Scheme 24
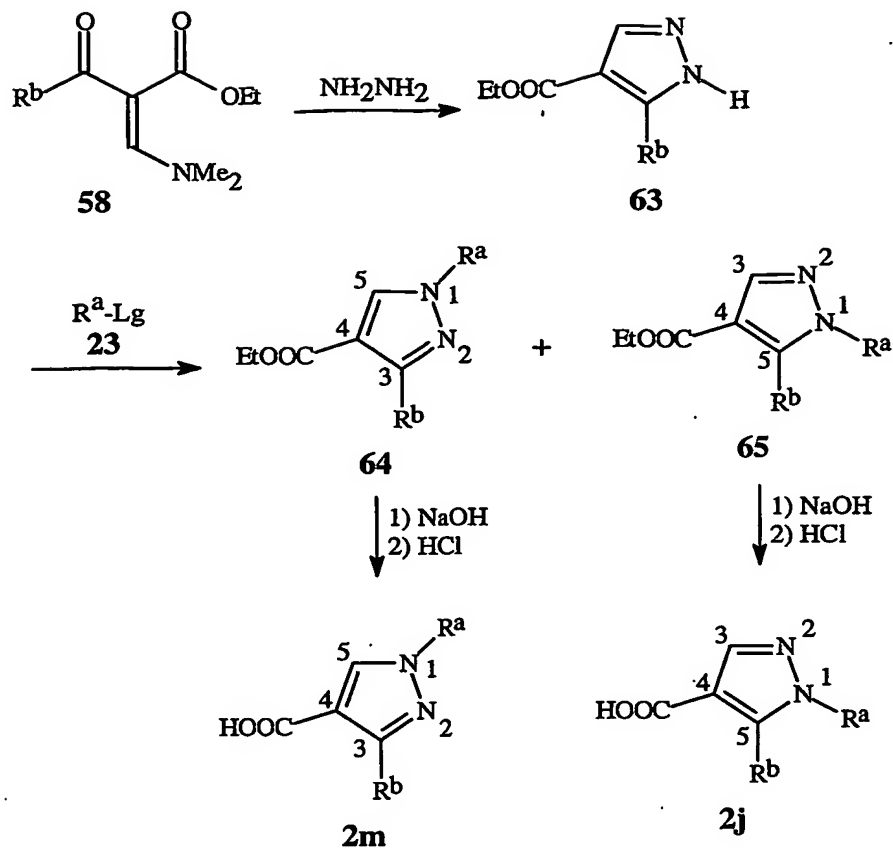
Of note is the synthesis of pyridinylpyrazole acids of Formula **2n**, a subset of the acids of Formula **2m** wherein R^b is a substituted 2-pyridinyl and attached to the 3-position of the pyrazole ring, as well as an alternative synthesis of Formula **2k**, is depicted in Scheme 25. In Formula **2n** and **2k** the substituent R^c is, for example, R^7 and is notably hydrogen and halogen. This synthesis is conducted according to the general synthesis described in Scheme 24.

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Scheme 25
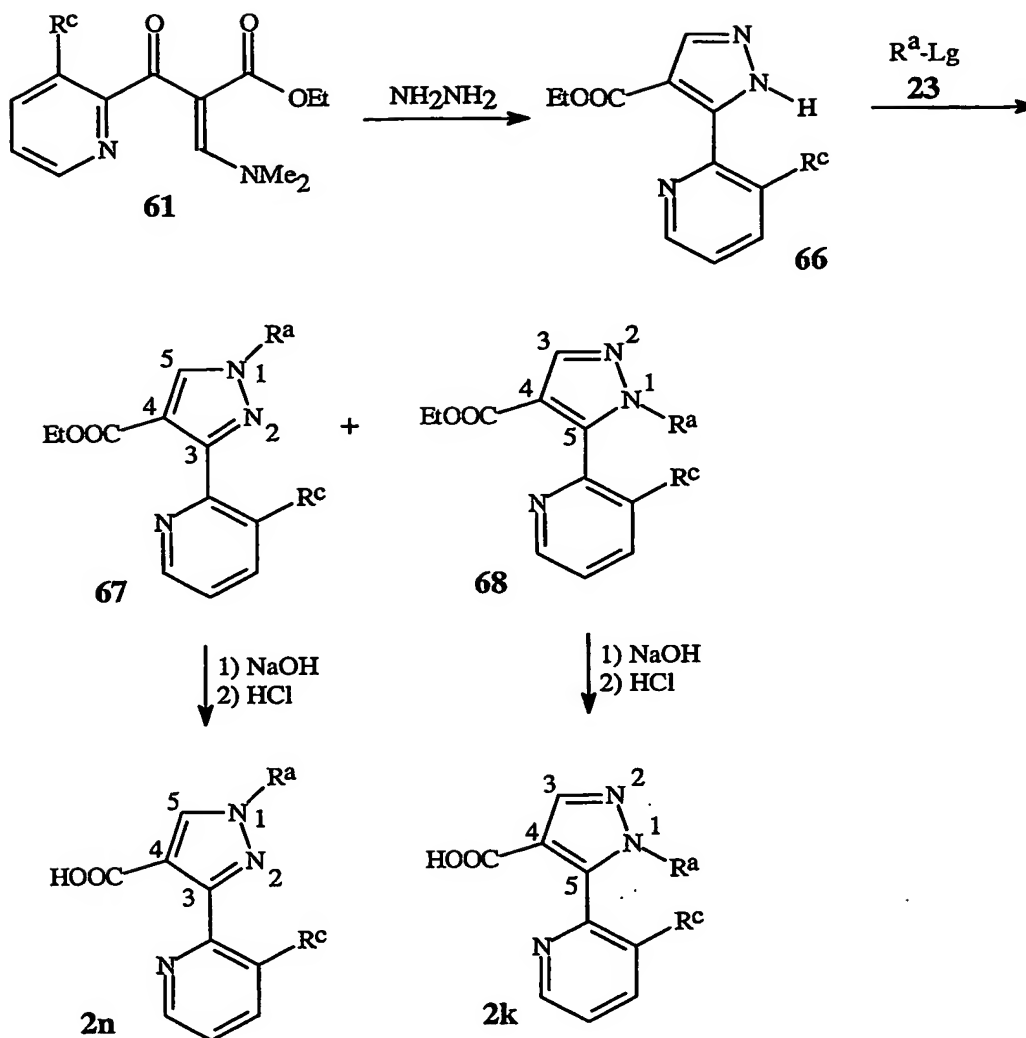
A general synthesis of pyrrole acids of Formula **2o** is depicted in Scheme 26. Substituent groups R^a include, for example, alkyl, haloalkyl, and optionally substituted aromatic and heteroaromatic rings. Treatment of a compound of Formula **69** with 2,5-dimethoxytetrahydrofuran (**70**) affords a pyrrole of Formula **71**. Formylation of the pyrrole **71** to provide the aldehyde of Formula **72** can be accomplished by using standard Vilsmeier-Haack formylation conditions, such as *N,N*-dimethylformamide (DMF) and phosphorus oxychloride. Halogenation of the compound of Formula **72** with *N*-halosuccinimides (NXS) such as *N*-chlorosuccinimide or *N*-bromosuccinimide occurs preferentially at the 4-position of the pyrrole ring. Oxidation of the halogenated aldehyde affords the pyrrole acid of Formula **2o**. The oxidation can be accomplished by using a variety of standard oxidation conditions.

40

Scheme 26
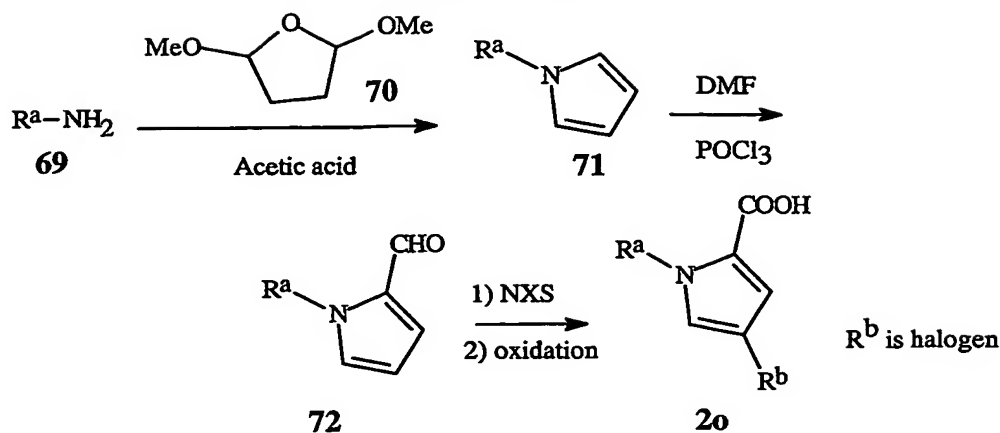
The synthesis of certain pyridinylpyrrole acids of Formula **2p** is depicted in Scheme 27. The compound of Formula **74**, 3-chloro-2-aminopyridine, is a known compound (see *J. Heterocycl. Chem.* **1987**, *24*(5), 1313–16). A convenient preparation of **74** from the 2-aminopyridine of Formula **73** involves protection, ortho-metallation, chlorination and subsequent deprotection. The remaining synthesis is conducted according to the general synthesis described in Scheme 26.

Scheme 27
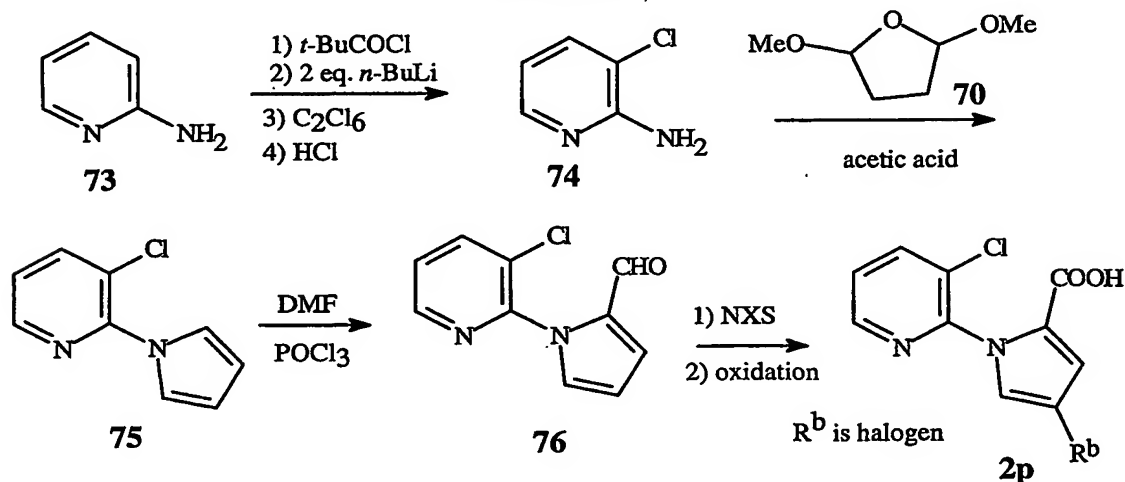
It is believed that one skilled in the art using the preceding description can utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative, and not limiting of the disclosure in any way whatsoever. Percentages are by weight except for chromatographic solvent mixtures or where otherwise indicated. Parts and percentages for chromatographic solvent mixtures are by volume unless otherwise indicated. ^{1}H NMR spectra are reported in ppm downfield from tetramethylsilane; "s" means singlet, "d" means doublet, "t" means triplet, "q" means quartet, "m" means multiplet, "dd" means doublet of doublets, "dt" means doublet of triplets, and

"br s" means broad singlet. Quantitative HPLC of the product was performed using an Ace C18 or C4 Ultra Inert® chromatography column (reversed phase column manufactured by MacMod Analytical Inc., Chadds Ford, PA 19317) (3 μm particle size, 4.6 mm × 15 cm, eluent 5-80% acetonitrile/ pH 3 phosphate buffer).

5   EXAMPLE 1

Preparation of 2-[3-bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazol-5-yl]-6-chloro-8-methyl-4H-3,1-benzoxazin-4-one

To a solution of methanesulfonyl chloride (5.0 mL, 7.4 g, 65 mmol) in acetonitrile (55 mL) at –5 °C was added dropwise a solution of 3-bromo-1-(3-chloro-2-pyridinyl)-1H-

10   pyrazole-5-carboxylic acid (see WO 03/015519 for preparation) (93.6% purity, 16.16 g, 50.0 mmol) and 3-picoline (8.3 mL, 7.9 g, 85 mmol) in acetonitrile (50 mL) over five minutes while maintaining the temperature at about –5 to 0 °C. A slurry formed during the addition. The mixture was stirred for 5 minutes at this temperature, and then 6-chloro-8-methyl-1H-benzo[d][1,3]oxazine-2,4-dione (99.0% purity, 11.22 g, 52.5 mmol) was added all at once,

15   and the residue was rinsed with acetonitrile (10 mL). To the reaction mixture was added 3-picoline (8.3 mL, 7.9 g, 85 mmol) dropwise in 5 minutes at –5 to 0 °C. After stirring for 15 minutes at –5 to 0 °C, the reaction mixture was heated to 50 °C and stirred 4 hours. Then the reaction mixture was cooled to room temperature, water (30 mL) was added dropwise and the mixture was stirred 15 minutes. The mixture was filtered, and the solids were re-slurried

20   sequentially with 4:1 acetonitrile–water (2 × 40 mL) and acetonitrile (3 × 40 mL), and then dried under nitrogen to afford the title product as a light yellow powder, 20.95 g (93.6% purity by HPLC, 86.7% yield calculated based on the purity).

^{1}H NMR (DMSO-d_6) δ 1.72 (s, 3H) 7.52 (s, 1H), 7.74–7.80 (m, 2H), 7.89 (m, 1H), 8.34 (dd, 1H, J = 8.4, 0.9 Hz), 8.62 (dd, 1H, J = 4.5, 0.9 Hz).

25   EXAMPLE 2

Preparation of 2-[3-bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazol-5-yl]-6-chloro-8-methyl-4H-3,1-benzoxazin-4-one by inverse addition

To a mixture of 3-bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carboxylic acid (see WO 03/015519 for preparation) (93.6% purity, 16.16 g, 50.0 mmol), 6-chloro-8-methyl-

30   1H-benzo[d][1,3]oxazine-2,4-dione (99.0% purity, 11.22 g, 52.5 mmol), and 3-picoline (16.5 mL, 15.8 g, 170 mmol) in acetonitrile (65 mL) at about –5 °C was added dropwise methanesulfonyl chloride (5.0 mL, 7.4 g, 65 mmol) in acetonitrile (15 mL). After 15 minutes at –5 to 0 °C, the reaction mixture was heated to 50 °C for 4 hours. The reaction mixture was then cooled to room temperature, water (20 mL) was added dropwise, and the

35   reaction mixture was stirred 15 minutes. The mixture was filtered, and the solids were washed sequentially with 4:1 acetonitrile–water (2 × 35 mL) and acetonitrile (3 × 35 mL),

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and dried under nitrogen to afford the title product as a light yellow powder, 20.55 g (94.4% purity by HPLC, 85.8% yield calculated based on the purity).

EXAMPLE 3

Preparation of 2-[3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]-6-cyano-8-methyl-4*H*-3,1-benzoxazin-4-one by inverse addition

A mixture of 3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxylic acid (97.9% purity, 3.09 g, 10.0 mmol), 6-cyano-8-methyl-1*H*-benzo[d][1,3]oxazine-2,4-dione (96.3% purity, 2.10 g, 10.0 mmol) and 3-picoline (3.30 mL, 3.16 g, 34 mmol) in acetonitrile (65 mL) was cooled to about –5 °C. Then methanesulfonyl chloride (1.0 mL, 1.5 g, 13 mmol) in acetonitrile (3 mL) was added dropwise at –5 to 0 °C. After 15 minutes at –5 to 0 °C, the reaction mixture was heated to 50 °C for 4 hours. The reaction mixture was then cooled to room temperature, water (4 mL) was added dropwise, and the reaction mixture was stirred 15 minutes. The mixture was filtered, and the solids were washed sequentially with 4:1 acetonitrile–water (2 × 2 mL) and acetonitrile (3 × 2 mL), and dried under nitrogen to afford the title product as a pale green powder, 3.71 g (94.2% purity by HPLC, 82.0% yield calculated based on the purity), melting at 263 – 267 °C.

^{1}H NMR (DMSO-d_6) δ 1.73 (s, 3H) 7.59 (s, 1H), 7.77 (dd, 1H, J = 8.2, 4.6 Hz), 8.09 (m, 1H), 8.32-8.40 (m, 2H), 8.63 (dd, 1H, J = 4.8, 1.5 Hz).

EXAMPLE 4

Preparation of 3-bromo-*N*-[4-chloro-2-methyl-6-[(1-methylamino)carbonyl]-phenyl]-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxamide in one pot

To a mixture of 3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazole-5-carboxylic acid (see WO 03/015519 for preparation) (93.6% purity, 16.16 g, 50.0 mmol), 6-chloro-8-methyl-1*H*-benzo[d][1,3]oxazine-2,4-dione (99.0% purity, 11.22 g, 52.5 mmol), and 3-picoline (16.5 mL, 15.8 g, 170 mmol) in acetonitrile (65 mL) at –5 °C was added dropwise methanesulfonyl chloride (5.0 mL, 7.4 g, 65 mmol) in acetonitrile (15 mL). After stirring 15 minutes at –5 to 0 °C, the mixture was heated to 50 °C for 4 hours. The reaction mixture was then cooled to room temperature, water (29 mL) was added dropwise, and the reaction mixture was stirred 15 minutes. Then 40% aqueous methylamine (20.0 mL, 17.9 g, 231 mmol) was added all at once, and the reaction mixture was stirred overnight at room temperature. The mixture was filtered, and the solids were washed sequentially with 2:1 acetonitrile–water (2 × 30 mL) and acetonitrile (3 × 30 mL), and dried under nitrogen to afford the title product as a light yellow powder, 22.44 g (95.5% purity by HPLC, 88.7% yield calculated based on the purity).

^{1}H NMR (CDCl$_3$) δ 2.18 (s, 3H), 2.95 (s, 3H), 6.21 (m, 1H), 7.10 (s, 1H), 7.24 (m, 2H), 7.39 (m, 1H), 7.80 (d, 1H), 8.45 (d, 1H).

By the methods and procedures described herein together with methods known in the art, the following compounds of Table 1 can be prepared.

TABLE 1
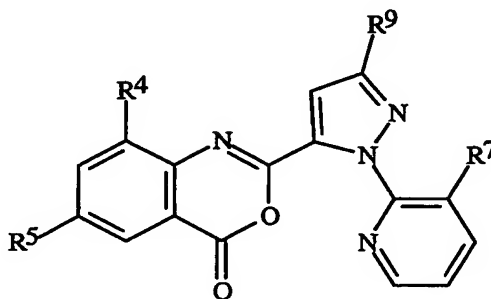
R^4	R^5	R^9	R^7	R^4	R^5	R^9	R^7	R^4	R^5	R^9	R^7
CH_3	F	CF_3	Cl	Cl	F	CF_3	Cl	CH_3	F	OCH_2CF_3	Cl
CH_3	F	CF_3	Br	Cl	F	CF_3	Br	CH_3	F	OCH_2CF_3	Br
CH_3	F	Cl	Cl	Cl	F	Cl	Cl	CH_3	F	$OCHF_2$	Cl
CH_3	F	Cl	Br	Cl	F	Cl	Br	CH_3	F	$OCHF_2$	Br
CH_3	F	Br	Cl	Cl	F	Br	Cl	Cl	F	OCH_2CF_3	Cl
CH_3	F	Br	Br	Cl	F	Br	Br	Cl	F	OCH_2CF_3	Br
CH_3	Cl	CF_3	Cl	Cl	Cl	CF_3	Cl	Cl	F	$OCHF_2$	Cl
CH_3	Cl	CF_3	Br	Cl	Cl	CF_3	Br	Cl	F	$OCHF_2$	Br
CH_3	Cl	Cl	Cl	Cl	Cl	Cl	Cl	CH_3	Cl	OCH_2CF_3	Cl
CH_3	Cl	Cl	Br	Cl	Cl	Cl	Br	CH_3	Cl	OCH_2CF_3	Br
CH_3	Cl	Br	Cl	Cl	Cl	Br	Cl	CH_3	Cl	$OCHF_2$	Cl
CH_3	Cl	Br	Br	Cl	Cl	Br	Br	CH_3	Cl	$OCHF_2$	Br
CH_3	Br	CF_3	Cl	Cl	Br	CF_3	Cl	Cl	Cl	OCH_2CF_3	Cl
CH_3	Br	CF_3	Br	Cl	Br	CF_3	Br	Cl	Cl	OCH_2CF_3	Br
CH_3	Br	Cl	Cl	Cl	Br	Cl	Cl	Cl	Cl	$OCHF_2$	Cl
CH_3	Br	Cl	Br	Cl	Br	Cl	Br	Cl	Cl	$OCHF_2$	Br
CH_3	Br	Br	Cl	Cl	Br	Br	Cl	CH_3	Br	OCH_2CF_3	Cl
CH_3	Br	Br	Br	Cl	Br	Br	Br	CH_3	Br	OCH_2CF_3	Br
CH_3	I	CF_3	Cl	Cl	I	CF_3	Cl	CH_3	Br	$OCHF_2$	Cl
CH_3	I	CF_3	Br	Cl	I	CF_3	Br	CH_3	Br	$OCHF_2$	Br
CH_3	I	Cl	Cl	Cl	I	Cl	Cl	Cl	Br	OCH_2CF_3	Cl
CH_3	I	Cl	Br	Cl	I	Cl	Br	Cl	Br	OCH_2CF_3	Br
CH_3	I	Br	Cl	Cl	I	Br	Cl	Cl	Br	$OCHF_2$	Cl
CH_3	I	Br	Br	Cl	I	Br	Br	Cl	Br	$OCHF_2$	Br
CH_3	CF_3	CF_3	Cl	Cl	CF_3	CF_3	Cl	Cl	I	OCH_2CF_3	Cl
CH_3	CF_3	CF_3	Br	Cl	CF_3	CF_3	Br	Cl	I	OCH_2CF_3	Br

R4	R5	R9	R7	R4	R5	R9	R7	R4	R5	R9	R7
CH3	CF3	Cl	Cl	Cl	CF3	Cl	Cl	Cl	I	OCHF2	Cl
CH3	CF3	Cl	Br	Cl	CF3	Cl	Br	Cl	I	OCHF2	Br
CH3	CF3	Br	Cl	Cl	CF3	Br	Cl	CH3	I	OCH2CF3	Cl
CH3	CF3	Br	Br	Cl	CF3	Br	Br	CH3	I	OCH2CF3	Br
CH3	Cl	Cl	Cl	Cl	Cl	Cl	Cl	CH3	I	OCHF2	Cl
F	F	CF3	Cl	Br	F	CF3	Cl	CH3	I	OCHF2	Br
F	F	CF3	Br	Br	F	CF3	Br	Cl	CF3	OCH2CF3	Cl
F	F	Cl	Cl	Br	F	Cl	Cl	Cl	CF3	OCH2CF3	Br
F	F	Cl	Br	Br	F	Cl	Br	Cl	CF3	OCHF2	Cl
F	F	Br	Cl	Br	F	Br	Cl	Cl	CF3	OCHF2	Br
F	F	Br	Br	Br	F	Br	Br	CH3	CF3	OCH2CF3	Cl
F	Cl	CF3	Cl	Br	Cl	CF3	Cl	CH3	CF3	OCH2CF3	Br
F	Cl	CF3	Br	Br	Cl	CF3	Br	CH3	CF3	OCHF2	Cl
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F	Cl	Br	Br	Br	Cl	Br	Br	F	F	OCH2CF3	Cl
F	Br	CF3	Cl	Br	Br	CF3	Cl	F	F	OCH2CF3	Br
F	Br	CF3	Br	Br	Br	CF3	Br	Br	Cl	OCH2CF3	Cl
F	Br	Cl	Cl	Br	Br	Cl	Cl	Br	Cl	OCH2CF3	Br
F	Br	Cl	Br	Br	Br	Cl	Br	F	Cl	OCH2CF3	Cl
F	Br	Br	Cl	Br	Br	Br	Cl	F	Cl	OCH2CF3	Br
F	Br	Br	Br	Br	Br	Br	Br	Br	Br	OCH2CF3	Cl
F	I	CF3	Cl	Br	I	CF3	Cl	Br	Br	OCH2CF3	Br
F	I	CF3	Br	Br	I	CF3	Br	F	Br	OCH2CF3	Cl
F	I	Cl	Cl	Br	I	Cl	Cl	F	Br	OCH2CF3	Br
F	I	Cl	Br	Br	I	Cl	Br	F	Br	OCHF2	Cl
F	I	Br	Cl	Br	I	Br	Cl	F	Br	OCHF2	Br
F	I	Br	Br	Br	I	Br	Br	Br	I	OCH2CF3	Cl
F	CF3	CF3	Cl	Br	CF3	CF3	Cl	Br	I	OCH2CF3	Br
F	CF3	CF3	Br	Br	CF3	CF3	Br	Br	I	OCHF2	Cl
F	CF3	Cl	Cl	Br	CF3	Cl	Cl	Br	I	OCHF2	Br
F	CF3	Cl	Br	Br	CF3	Cl	Br	F	I	OCH2CF3	Cl
F	CF3	Br	Cl	Br	CF3	Br	Cl	F	I	OCH2CF3	Br
F	CF3	Br	Br	Br	CF3	Br	Br	Br	CF3	OCH2CF3	Cl
F	F	OCHF2	Cl	Br	F	OCHF2	Cl	Br	CF3	OCH2CF3	Br
F	F	OCHF2	Br	Br	F	OCHF2	Br	Br	CF3	OCHF2	Cl

R^4	R^5	R^9	R^7	R^4	R^5	R^9	R^7	R^4	R^5	R^9	R^7
F	Cl	$OCHF_2$	Cl	Br	Cl	$OCHF_2$	Cl	Br	CF_3	$OCHF_2$	Br
F	Cl	$OCHF_2$	Br	Br	Cl	$OCHF_2$	Br	F	CF_3	OCH_2CF_3	Cl
F	I	$OCHF_2$	Cl	Br	Br	$OCHF_2$	Cl	F	CF_3	OCH_2CF_3	Br
F	I	$OCHF_2$	Br	Br	Br	$OCHF_2$	Br	F	CF_3	$OCHF_2$	Cl
CH_3	CN	CF_3	Cl	Cl	CN	CF_3	Cl	F	CF_3	$OCHF_2$	Br
CH_3	CN	CF_3	Br	Cl	CN	CF_3	Br	Br	CN	CF_3	Cl
CH_3	CN	Cl	Cl	Cl	CN	Cl	Cl	Br	CN	CF_3	Br
CH_3	CN	Cl	Br	Cl	CN	Cl	Br	Br	CN	Cl	Cl
CH_3	CN	Br	Cl	Cl	CN	Br	Cl	Br	CN	Cl	Br
CH_3	CN	Br	Br	Cl	CN	Br	Br	Br	CN	Br	Cl
CH_3	CN	OCH_2CF_3	Cl	Cl	CN	OCH_2CF_3	Cl	Br	CN	Br	Br
CH_3	CN	OCH_2CF_3	Br	Cl	CN	OCH_2CF_3	Br	Br	CN	$OCHF_2$	Cl
CH_3	CN	$OCHF_2$	Cl	Cl	CN	$OCHF_2$	Cl	Br	CN	$OCHF_2$	Br
CH_3	CN	$OCHF_2$	Br	Cl	CN	$OCHF_2$	Br	Br	CN	OCH_2CF_3	Cl
F	CN	CF_3	Cl	F	CN	Cl	Cl	Br	CN	OCH_2CF_3	Br
F	CN	CF_3	Br	F	CN	Cl	Br	F	CN	OCH_2CF_3	Cl
F	CN	Br	Cl	F	CN	$OCHF_2$	Cl	F	CN	OCH_2CF_3	Br
F	CN	Br	Br	F	CN	$OCHF_2$	Br				

The fused oxazinone preparation method of the present invention can be used to prepare a wide variety of compounds of Formula 1 that are useful as intermediates for the preparation of crop protection agents, pharmaceuticals and other fine chemicals. Exhibit 4 lists examples of fused oxazinones which can be prepared according to the method of the present invention from corresponding carboxylic acids of Formula 2 and isatoic anhydrides of Formula 5, including fused oxazinones which are useful in the preparation of products having antiviral, nematocidal, microbiocidal, acaricidal, fungicidal and herbicidal utility. These examples are to be construed as illustrative, but not limiting, of the diverse scope of applicability of the method of the present invention. Other compounds preparable according to the method of the present invention may be useful for preparation of pharmaceutical products having additional utilities, such as anti-tumor activity, anti-allergenic activity, protease inhibition, etc.

Exhibit 4

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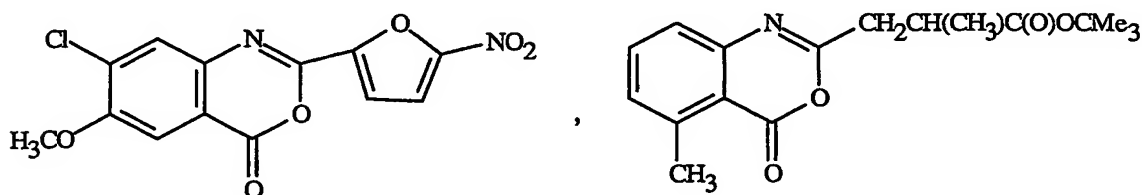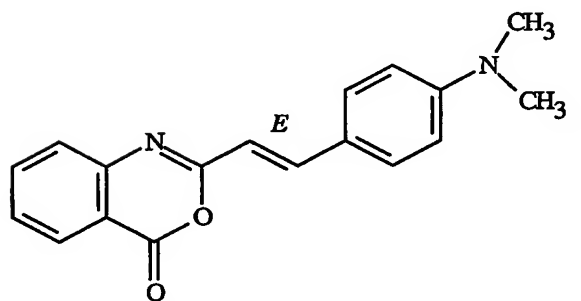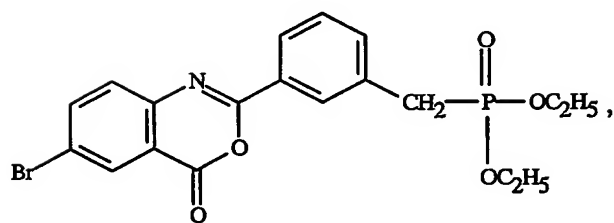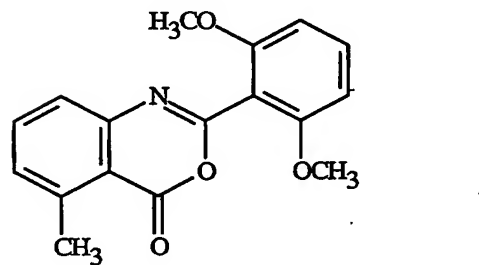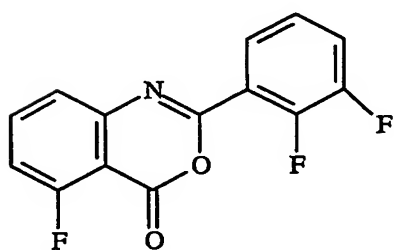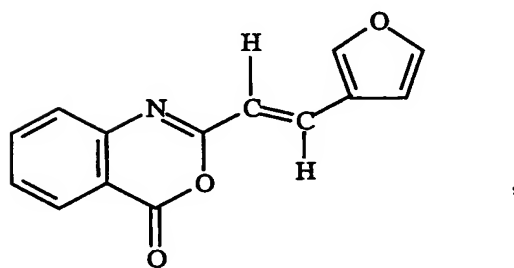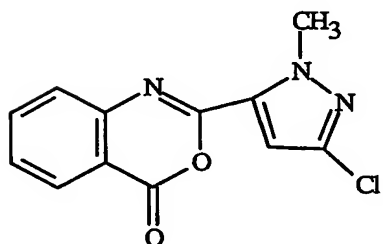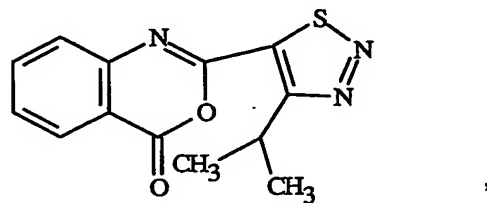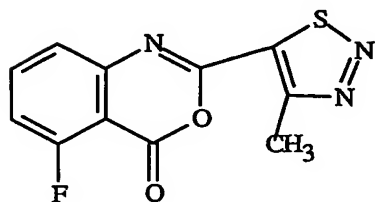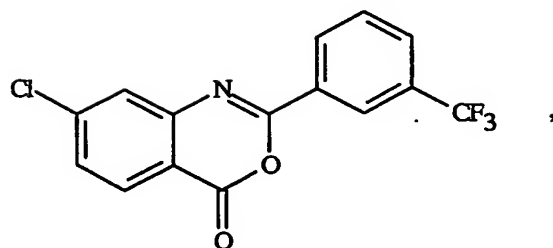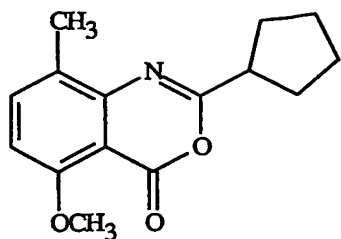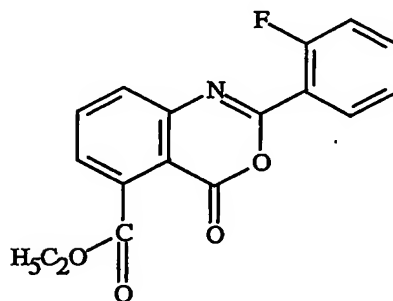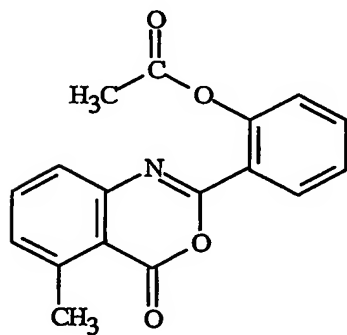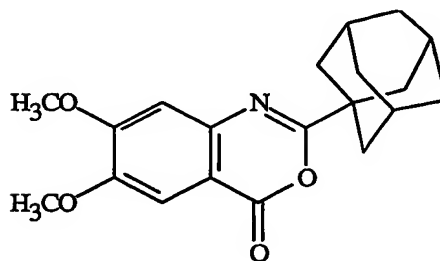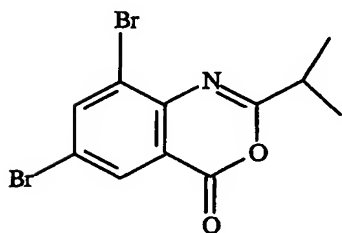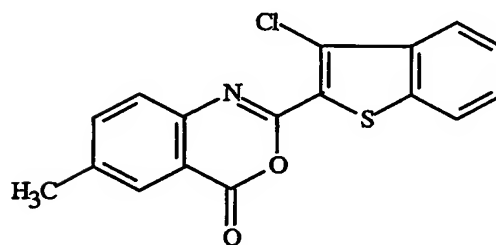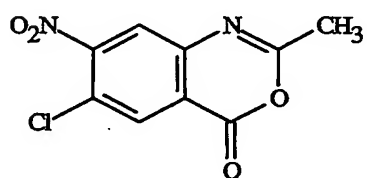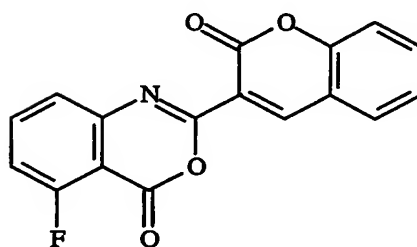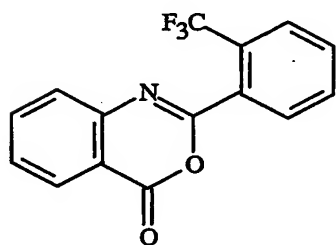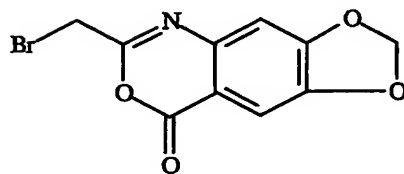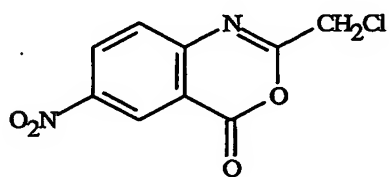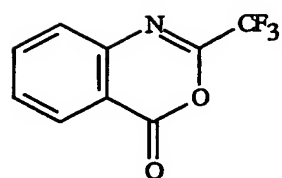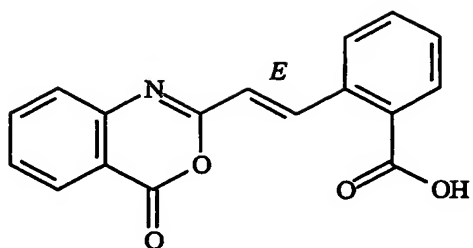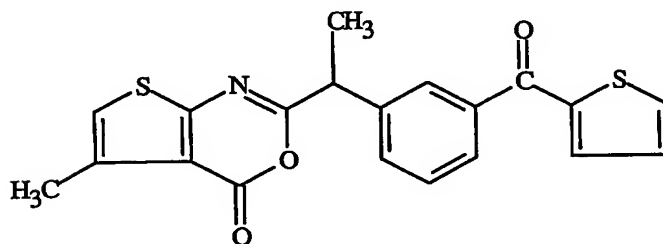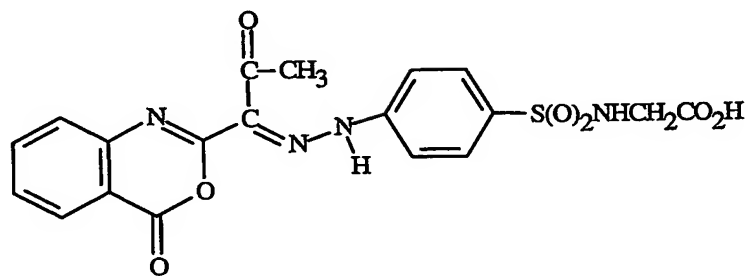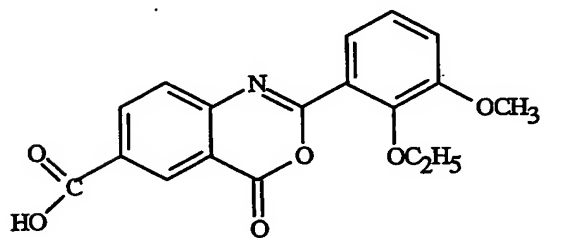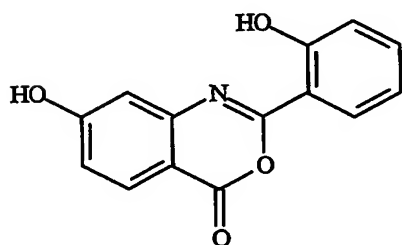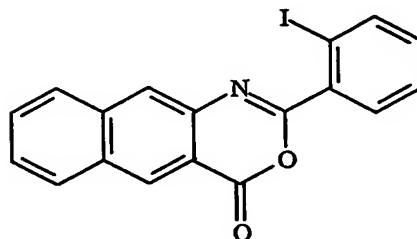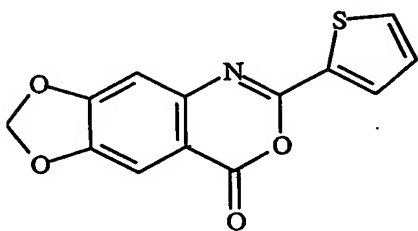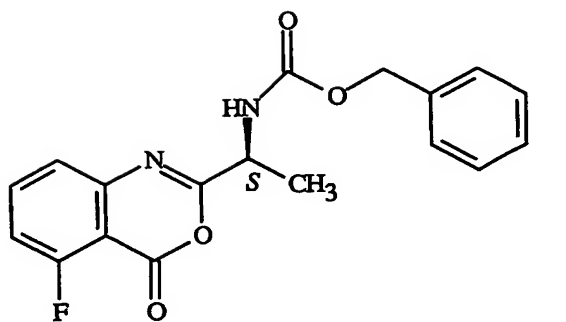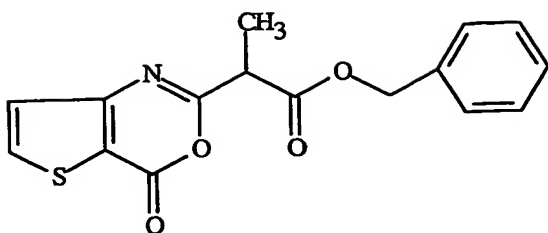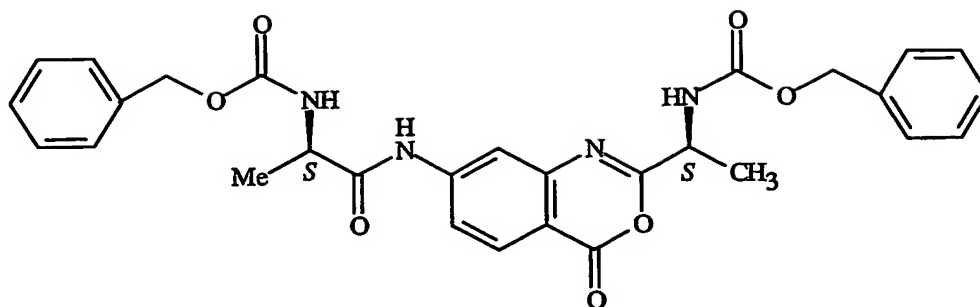
Furthermore as shown in Scheme A, compounds of Formula **1** can be used to prepare compounds of Formula **II** by reaction with nucleophiles, optionally in the presence of additional base.

Scheme A
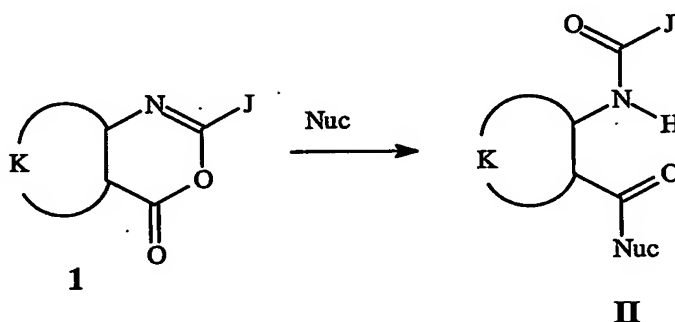
As shown in Scheme 28, reaction of Formula **1** with nucleophiles of Formula **77** wherein R^d can be an optionally substituted carbon moiety (i.e. alcohols) leads to esters of Formula **IIa**. Reaction of Formula **1** with nucleophiles of Formula **78** wherein R^e and R^f can be independently H or an optionally substituted carbon moiety (i.e. ammonia, primary amines or secondary amines) leads to amides of Formula **IIb**.

Scheme 28

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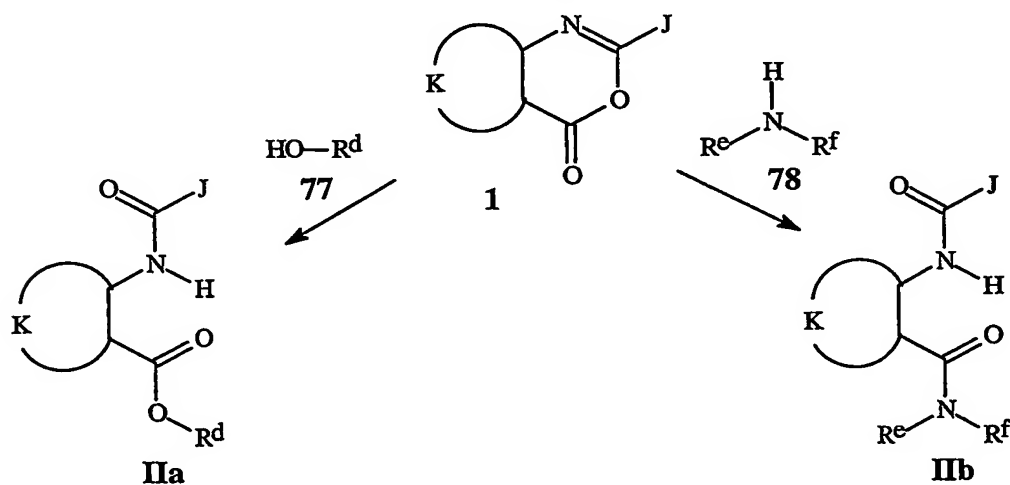
Typical procedures for preparation of compounds of Formula **IIb** involve combination of an amine of Formula **78** with the fused oxazinone of Formula **1**. The reaction can be run neat or in a variety of suitable solvents including acetonitrile, tetrahydrofuran, diethyl ether, dichloromethane or chloroform with optimum temperatures ranging from room temperature to the reflux temperature of the solvent. For references to the chemistry of heterocyclic fused oxazinones see Jakobsen et al., *Biorganic and Medicinal Chemistry* **2000**, *8*, 2803–2812 and references cited therein.

As a particular example, compounds of Formula **1a** are useful for preparing compounds of Formula **III**

III

wherein

X is N or CR^6;

Y is N or CH;

R^1 is H;

R^2 is H or CH_3;

R^3 is C_1–C_6 alkyl;

R^4 is C_1–C_4 alkyl or halogen;

R^5 is H, C_1–C_4 alkyl, C_1–C_4 haloalkyl, CN or halogen;

R^6 and R^7 are independently H, C_1–C_4 alkyl, C_1–C_4 haloalkyl, halogen, CN or C_1–C_4 haloalkoxy;

R^8 is H, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, C_3–C_6 cycloalkyl, C_1–C_4 haloalkyl, C_2–C_4 haloalkenyl, C_2–C_4 haloalkynyl, C_3–C_6 halocycloalkyl, halogen, CN, NO_2, C_1–C_4 alkoxy, C_1–C_4 haloalkoxy, C_1–C_4 alkylthio, C_1–C_4 alkylsulfinyl, C_1–C_4 alkylsulfonyl, C_1–C_4 alkylamino, C_2–C_8 dialkylamino, C_3–C_6 cycloalkylamino, (C_1–C_4 alkyl)(C_3–C_6 cycloalkyl)amino, C_2–C_4 alkylcarbonyl, C_2–C_6 alkoxycarbonyl, C_2–C_6 alkylaminocarbonyl, C_3–C_8 dialkylaminocarbonyl or C_3–C_6 trialkylsilyl;

R^9 is CF_3, OCF_3, $OCHF_2$, OCH_2CF_3, $S(O)_pCF_3$, $S(O)_pCHF_2$ or halogen; and

p is 0, 1 or 2.

Compounds of Formula **III** are useful as insecticides, as described, for example, in PCT Publication No. WO 01/70671, published September 27, 2001, as well as in U.S. Patent

Application 60/324,173, filed September 21, 2001, U.S. Patent Application 60/323,941, filed September 21, 2001 and U.S. Patent Application 60/369,661, filed April 2, 2002. The preparation of compounds of Formula 1a and Formula III is described in U.S. Patent Application 60/400356, filed July 31, 2002, and U.S. Patent Application 60/446451, filed February 11, 2003 and hereby incorporated herein in their entirety by reference; as well as in U.S. Patent Application 60/369,659, filed April 2, 2002 and U.S. Patent Application 60/369,660, filed April 2, 2002.

Compounds of Formula III can be prepared by the reaction of benzoxazinones of Formula 1a with C_1–C_6 alkylamines and $(C_1$–C_6 alkyl)(methyl)amines of Formula 79 as outlined in Scheme 29.

<u>Scheme 29</u>
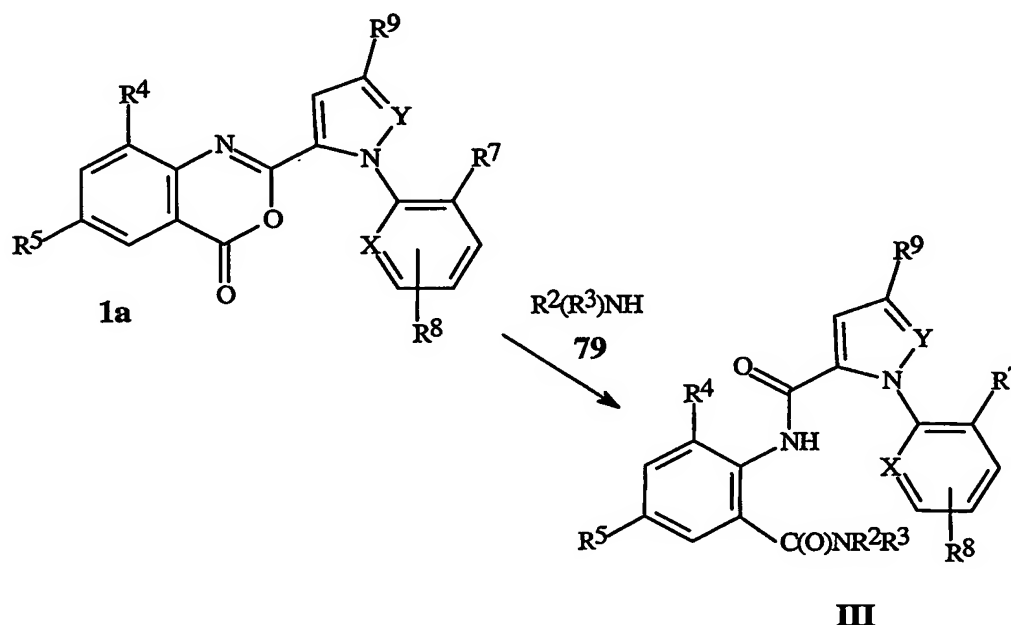
III

The reaction can be run neat or in a variety of suitable solvents including acetonitrile, tetrahydrofuran, diethyl ether, dichloromethane or chloroform with optimum temperatures ranging from room temperature to the reflux temperature of the solvent. The general reaction of benzoxazinones with amines to produce anthranilamides is well documented in the chemical literature. For a review of benzoxazinone chemistry see Jakobsen et al., *Biorganic and Medicinal Chemistry* **2000**, *8*, 2095–2103 and references cited within. See also Coppola, *J. Heterocyclic Chemistry* **1999**, *36*, 563–588.

Of note are methods for preparing compounds of Formula 1a or Formula III wherein R^9 is CF_3, OCF_3, $OCHF_2$, OCH_2CF_3 or halogen. Of particular note are methods for preparing compounds of Formula 1a or Formula III wherein R^9 is CF_3, $OCHF_2$, OCH_2CF_3, Cl or Br. Preferred are methods for preparing compounds of Formula 1a or Formula III wherein

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X is N;

Y is N;

R^2 is H or CH_3;

R^3 is C_1–C_4 alkyl;

5   R^4 is CH_3, F, Cl or Br;

R^5 is CF_3, CN, F, Cl, Br or I;

R^7 is Cl or Br;

R^8 is H, and

R^9 is CF_3, $OCHF_2$, OCH_2CF_3, Cl or Br.

10   Also of particular note are compounds of Formula **III** wherein R^9 is $OCHF_2$.

By the procedures described herein together with methods known in the art, the following compounds of Table 2 can be prepared. The following abbreviations are used in the Tables which follow: *t* means tertiary, *s* means secondary, *n* means normal, *i* means iso, Me means methyl, Et means ethyl, Pr means propyl, *i*-Pr means isopropyl, and Bu means

15   butyl.

TABLE 2
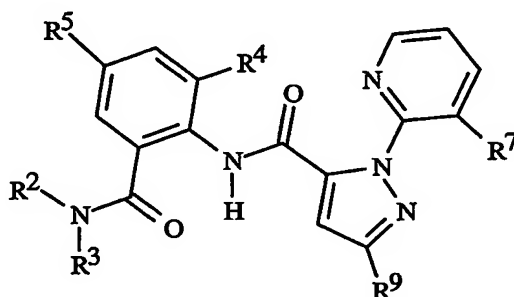
R^4	R^5	R^9	R^3	R^2	R^7	R^4	R^5	R^9	R^3	R^2	R^7
CH_3	F	CF_3	Me	H	Cl	Cl	F	CF_3	Me	H	Cl
CH_3	F	CF_3	Et	H	Cl	Cl	F	CF_3	Et	H	Cl
CH_3	F	CF_3	*i*-Pr	H	Cl	Cl	F	CF_3	*i*-Pr	H	Cl
CH_3	F	CF_3	*t*-Bu	H	Cl	Cl	F	CF_3	*t*-Bu	H	Cl
CH_3	F	CF_3	Me	Me	Cl	Cl	F	CF_3	Me	Me	Cl
CH_3	F	CF_3	Me	H	Br	Cl	F	CF_3	Me	H	Br
CH_3	F	CF_3	Et	H	Br	Cl	F	CF_3	Et	H	Br
CH_3	F	CF_3	*i*-Pr	H	Br	Cl	F	CF_3	*i*-Pr	H	Br
CH_3	F	CF_3	*t*-Bu	H	Br	Cl	F	CF_3	*t*-Bu	H	Br
CH_3	F	CF_3	Me	Me	Br	Cl	F	CF_3	Me	Me	Br
CH_3	F	Cl	Me	H	Cl	Cl	F	Cl	Me	H	Cl
CH_3	F	Cl	Et	H	Cl	Cl	F	Cl	Et	H	Cl

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R4	R5	R9	R3	R2	R7	R4	R5	R9	R3	R2	R7
CH3	F	Cl	i-Pr	H	Cl	Cl	F	Cl	i-Pr	H	Cl
CH3	F	Cl	t-Bu	H	Cl	Cl	F	Cl	t-Bu	H	Cl
CH3	F	Cl	Me	Me	Cl	Cl	F	Cl	Me	Me	Cl
CH3	F	Cl	Me	H	Br	Cl	F	Cl	Me	H	Br
CH3	F	Cl	Et	H	Br	Cl	F	Cl	Et	H	Br
CH3	F	Cl	i-Pr	H	Br	Cl	F	Cl	i-Pr	H	Br
CH3	F	Cl	t-Bu	H	Br	Cl	F	Cl	t-Bu	H	Br
CH3	F	Cl	Me	Me	Br	Cl	F	Cl	Me	Me	Br
CH3	F	Br	Me	H	Cl	Cl	F	Br	Me	H	Cl
CH3	F	Br	Et	H	Cl	Cl	F	Br	Et	H	Cl
CH3	F	Br	i-Pr	H	Cl	Cl	F	Br	i-Pr	H	Cl
CH3	F	Br	t-Bu	H	Cl	Cl	F	Br	t-Bu	H	Cl
CH3	F	Br	Me	Me	Cl	Cl	F	Br	Me	Me	Cl
CH3	F	Br	Me	H	Br	Cl	F	Br	Me	H	Br
CH3	F	Br	Et	H	Br	Cl	F	Br	Et	H	Br
CH3	F	Br	i-Pr	H	Br	Cl	F	Br	i-Pr	H	Br
CH3	F	Br	t-Bu	H	Br	Cl	F	Br	t-Bu	H	Br
CH3	F	Br	Me	Me	Br	Cl	F	Br	Me	Me	Br
CH3	F	OCH2CF3	Me	H	Cl	Cl	F	OCH2CF3	Me	H	Cl
CH3	F	OCH2CF3	Et	H	Cl	Cl	F	OCH2CF3	Et	H	Cl
CH3	F	OCH2CF3	i-Pr	H	Cl	Cl	F	OCH2CF3	i-Pr	H	Cl
CH3	F	OCH2CF3	t-Bu	H	Cl	Cl	F	OCH2CF3	t-Bu	H	Cl
CH3	F	OCH2CF3	Me	Me	Cl	Cl	F	OCH2CF3	Me	Me	Cl
CH3	F	OCH2CF3	Me	H	Br	Cl	F	OCH2CF3	Me	H	Br
CH3	F	OCH2CF3	Et	H	Br	Cl	F	OCH2CF3	Et	H	Br
CH3	F	OCH2CF3	i-Pr	H	Br	Cl	F	OCH2CF3	i-Pr	H	Br
CH3	F	OCH2CF3	t-Bu	H	Br	Cl	F	OCH2CF3	t-Bu	H	Br
CH3	F	OCH2CF3	Me	Me	Br	Cl	F	OCH2CF3	Me	Me	Br
CH3	Cl	CF3	Me	H	Cl	Cl	Cl	CF3	Me	H	Cl
CH3	Cl	CF3	Et	H	Cl	Cl	Cl	CF3	Et	H	Cl
CH3	Cl	CF3	i-Pr	H	Cl	Cl	Cl	CF3	i-Pr	H	Cl
CH3	Cl	CF3	t-Bu	H	Cl	Cl	Cl	CF3	t-Bu	H	Cl
CH3	Cl	CF3	Me	Me	Cl	Cl	Cl	CF3	Me	Me	Cl
CH3	Cl	CF3	Me	H	Br	Cl	Cl	CF3	Me	H	Br
CH3	Cl	CF3	Et	H	Br	Cl	Cl	CF3	Et	H	Br
CH3	Cl	CF3	i-Pr	H	Br	Cl	Cl	CF3	i-Pr	H	Br
CH3	Cl	CF3	t-Bu	H	Br	Cl	Cl	CF3	t-Bu	H	Br

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R⁴	R⁵	R⁹	R³	R²	R⁷	R⁴	R⁵	R⁹	R³	R²	R⁷
CH₃	Cl	CF₃	Me	Me	Br	Cl	Cl	CF₃	Me	Me	Br
CH₃	Cl	Cl	Me	H	Cl	Cl	Cl	Cl	Me	H	Cl
CH₃	Cl	Cl	Et	H	Cl	Cl	Cl	Cl	Et	H	Cl
CH₃	Cl	Cl	i-Pr	H	Cl	Cl	Cl	Cl	i-Pr	H	Cl
CH₃	Cl	Cl	t-Bu	H	Cl	Cl	Cl	Cl	t-Bu	H	Cl
CH₃	Cl	Cl	Me	Me	Cl	Cl	Cl	Cl	Me	Me	Cl
CH₃	Cl	Cl	Me	H	Br	Cl	Cl	Cl	Me	H	Br
CH₃	Cl	Cl	Et	H	Br	Cl	Cl	Cl	Et	H	Br
CH₃	Cl	Cl	i-Pr	H	Br	Cl	Cl	Cl	i-Pr	H	Br
CH₃	Cl	Cl	t-Bu	H	Br	Cl	Cl	Cl	t-Bu	H	Br
CH₃	Cl	Cl	Me	Me	Br	Cl	Cl	Cl	Me	Me	Br
CH₃	Cl	Br	Me	H	Cl	Cl	Cl	Br	Me	H	Cl
CH₃	Cl	Br	Et	H	Cl	Cl	Cl	Br	Et	H	Cl
CH₃	Cl	Br	i-Pr	H	Cl	Cl	Cl	Br	i-Pr	H	Cl
CH₃	Cl	Br	t-Bu	H	Cl	Cl	Cl	Br	t-Bu	H	Cl
CH₃	Cl	Br	Me	Me	Cl	Cl	Cl	Br	Me	Me	Cl
CH₃	Cl	Br	Me	H	Br	Cl	Cl	Br	Me	H	Br
CH₃	Cl	Br	Et	H	Br	Cl	Cl	Br	Et	H	Br
CH₃	Cl	Br	i-Pr	H	Br	Cl	Cl	Br	i-Pr	H	Br
CH₃	Cl	Br	t-Bu	H	Br	Cl	Cl	Br	·t-Bu	H	Br
CH₃	Cl	Br	Me	Me	Br	Cl	Cl	Br	Me	Me	Br
CH₃	Cl	OCH₂CF₃	Me	H	Cl	Cl	Cl	OCH₂CF₃	Me	H	Cl
CH₃	Cl	OCH₂CF₃	Et	H	Cl	Cl	Cl	OCH₂CF₃	Et	H	Cl
CH₃	Cl	OCH₂CF₃	i-Pr	H	Cl	Cl	Cl	OCH₂CF₃	i-Pr	H	Cl
CH₃	Cl	OCH₂CF₃	t-Bu	H	Cl	Cl	Cl	OCH₂CF₃	t-Bu	H	Cl
CH₃	Cl	OCH₂CF₃	Me	Me	Cl	Cl	Cl	OCH₂CF₃	Me	Me	Cl
CH₃	Cl	OCH₂CF₃	Me	H	Br	Cl	Cl	OCH₂CF₃	Me	H	Br
CH₃	Cl	OCH₂CF₃	Et	H	Br	Cl	Cl	OCH₂CF₃	Et	H	Br
CH₃	Cl	OCH₂CF₃	i-Pr	H	Br	Cl	Cl	OCH₂CF₃	i-Pr	H	Br
CH₃	Cl	OCH₂CF₃	t-Bu	H	Br	Cl	Cl	OCH₂CF₃	t-Bu	H	Br
CH₃	Cl	OCH₂CF₃	Me	Me	Br	Cl	Cl	OCH₂CF₃	Me	Me	Br
CH₃	Br	CF₃	Me	H	Cl	Cl	Br	CF₃	Me	H	Cl
CH₃	Br	CF₃	Et	H	Cl	Cl	Br	CF₃	Et	H	Cl
CH₃	Br	CF₃	i-Pr	H	Cl	Cl	Br	CF₃	i-Pr	H	Cl
CH₃	Br	CF₃	t-Bu	H	Cl	Cl	Br	CF₃	t-Bu	H	Cl
CH₃	Br	CF₃	Me	Me	Cl	Cl	Br	CF₃	Me	Me	Cl
CH₃	Br	CF₃	Me	H	Br	Cl	Br	CF₃	Me	H	Br

R4	R5	R9	R3	R2	R7	R4	R5	R9	R3	R2	R7
CH3	Br	CF3	Et	H	Br	Cl	Br	CF3	Et	H	Br
CH3	Br	CF3	i-Pr	H	Br	Cl	Br	CF3	i-Pr	H	Br
CH3	Br	CF3	t-Bu	H	Br	Cl	Br	CF3	t-Bu	H	Br
CH3	Br	CF3	Me	Me	Br	Cl	Br	CF3	Me	Me	Br
CH3	Br	Cl	Me	H	Cl	Cl	Br	Cl	Me	H	Cl
CH3	Br	Cl	Et	H	Cl	Cl	Br	Cl	Et	H	Cl
CH3	Br	Cl	i-Pr	H	Cl	Cl	Br	Cl	i-Pr	H	Cl
CH3	Br	Cl	t-Bu	H	Cl	Cl	Br	Cl	t-Bu	H	Cl
CH3	Br	Cl	Me	Me	Cl	Cl	Br	Cl	Me	Me	Cl
CH3	Br	Cl	Me	H	Br	Cl	Br	Cl	Me	H	Br
CH3	Br	Cl	Et	H	Br	Cl	Br	Cl	Et	H	Br
CH3	Br	Cl	i-Pr	H	Br	Cl	Br	Cl	i-Pr	H	Br
CH3	Br	Cl	t-Bu	H	Br	Cl	Br	Cl	t-Bu	H	Br
CH3	Br	Cl	Me	Me	Br	Cl	Br	Cl	Me	Me	Br
CH3	Br	Br	Me	H	Cl	Cl	Br	Br	Me	H	Cl
CH3	Br	Br	Et	H	Cl	Cl	Br	Br	Et	H	Cl
CH3	Br	Br	i-Pr	H	Cl	Cl	Br	Br	i-Pr	H	Cl
CH3	Br	Br	t-Bu	H	Cl	Cl	Br	Br	t-Bu	H	Cl
CH3	Br	Br	Me	Me	Cl	Cl	Br	Br	Me	Me	Cl
CH3	Br	Br	Me	H	Br	Cl	Br	Br	Me	H	Br
CH3	Br	Br	Et	H	Br	Cl	Br	Br	Et	H	Br
CH3	Br	Br	i-Pr	H	Br	Cl	Br	Br	i-Pr	H	Br
CH3	Br	Br	t-Bu	H	Br	Cl	Br	Br	t-Bu	H	Br
CH3	Br	Br	Me	Me	Br	Cl	Br	Br	Me	Me	Br
CH3	Br	OCH2CF3	Me	H	Cl	Cl	Br	OCH2CF3	Me	H	Cl
CH3	Br	OCH2CF3	Et	H	Cl	Cl	Br	OCH2CF3	Et	H	Cl
CH3	Br	OCH2CF3	i-Pr	H	Cl	Cl	Br	OCH2CF3	i-Pr	H	Cl
CH3	Br	OCH2CF3	t-Bu	H	Cl	Cl	Br	OCH2CF3	t-Bu	H	Cl
CH3	Br	OCH2CF3	Me	Me	Cl	Cl	Br	OCH2CF3	Me	Me	Cl
CH3	Br	OCH2CF3	Me	H	Br	Cl	Br	OCH2CF3	Me	H	Br
CH3	Br	OCH2CF3	Et	H	Br	Cl	Br	OCH2CF3	Et	H	Br
CH3	Br	OCH2CF3	i-Pr	H	Br	Cl	Br	OCH2CF3	i-Pr	H	Br
CH3	Br	OCH2CF3	t-Bu	H	Br	Cl	Br	OCH2CF3	t-Bu	H	Br
CH3	Br	OCH2CF3	Me	Me	Br	Cl	Br	OCH2CF3	Me	Me	Br
CH3	I	CF3	Me	H	Cl	Cl	I	CF3	Me	H	Cl
CH3	I	CF3	Et	H	Cl	Cl	I	CF3	Et	H	Cl
CH3	I	CF3	i-Pr	H	Cl	Cl	I	CF3	i-Pr	H	Cl

R^4	R^5	R^9	R^3	R^2	R^7	R^4	R^5	R^9	R^3	R^2	R^7
CH$_3$	I	CF$_3$	t-Bu	H	Cl	Cl	I	CF$_3$	t-Bu	H	Cl
CH$_3$	I	CF$_3$	Me	Me	Cl	Cl	I	CF$_3$	Me	Me	Cl
CH$_3$	I	CF$_3$	Me	H	Br	Cl	I	CF$_3$	Me	H	Br
CH$_3$	I	CF$_3$	Et	H	Br	Cl	I	CF$_3$	Et	H	Br
CH$_3$	I	CF$_3$	i-Pr	H	Br	Cl	I	CF$_3$	i-Pr	H	Br
CH$_3$	I	CF$_3$	t-Bu	H	Br	Cl	I	CF$_3$	t-Bu	H	Br
CH$_3$	I	CF$_3$	Me	Me	Br	Cl	I	CF$_3$	Me	Me	Br
CH$_3$	I	Cl	Me	H	Cl	Cl	I	Cl	Me	H	Cl
CH$_3$	I	Cl	Et	H	Cl	Cl	I	Cl	Et	H	Cl
CH$_3$	I	Cl	i-Pr	H	Cl	Cl	I	Cl	i-Pr	H	Cl
CH$_3$	I	Cl	t-Bu	H	Cl	Cl	I	Cl	t-Bu	H	Cl
CH$_3$	I	Cl	Me	Me	Cl	Cl	I	Cl	Me	Me	Cl
CH$_3$	I	Cl	Me	H	Br	Cl	I	Cl	Me	H	Br
CH$_3$	I	Cl	Et	H	Br	Cl	I	Cl	Et	H	Br
CH$_3$	I	Cl	i-Pr	H	Br	Cl	I	Cl	i-Pr	H	Br
CH$_3$	I	Cl	t-Bu	H	Br	Cl	I	Cl	t-Bu	H	Br
CH$_3$	I	Cl	Me	Me	Br	Cl	I	Cl	Me	Me	Br
CH$_3$	I	Br	Me	H	Cl	Cl	I	Br	Me	H	Cl
CH$_3$	I	Br	Et	H	Cl	Cl	I	Br	Et	H	Cl
CH$_3$	I	Br	i-Pr	H	Cl	Cl	I	Br	i-Pr	H	Cl
CH$_3$	I	Br	t-Bu	H	Cl	Cl	I	Br	t-Bu	H	Cl
CH$_3$	I	Br	Me	Me	Cl	Cl	I	Br	Me	Me	Cl
CH$_3$	I	Br	Me	H	Br	Cl	I	Br	Me	H	Br
CH$_3$	I	Br	Et	H	Br	Cl	I	Br	Et	H	Br
CH$_3$	I	Br	i-Pr	H	Br	Cl	I	Br	i-Pr	H	Br
CH$_3$	I	Br	t-Bu	H	Br	Cl	I	Br	t-Bu	H	Br
CH$_3$	I	Br	Me	Me	Br	Cl	I	Br	Me	Me	Br
CH$_3$	I	OCH$_2$CF$_3$	Me	H	Cl	Cl	I	OCH$_2$CF$_3$	Me	H	Cl
CH$_3$	I	OCH$_2$CF$_3$	Et	H	Cl	Cl	I	OCH$_2$CF$_3$	Et	H	Cl
CH$_3$	I	OCH$_2$CF$_3$	i-Pr	H	Cl	Cl	I	OCH$_2$CF$_3$	i-Pr	H	Cl
CH$_3$	I	OCH$_2$CF$_3$	t-Bu	H	Cl	Cl	I	OCH$_2$CF$_3$	t-Bu	H	Cl
CH$_3$	I	OCH$_2$CF$_3$	Me	Me	Cl	Cl	I	OCH$_2$CF$_3$	Me	Me	Cl
CH$_3$	I	OCH$_2$CF$_3$	Me	H	Br	Cl	I	OCH$_2$CF$_3$	Me	H	Br
CH$_3$	I	OCH$_2$CF$_3$	Et	H	Br	Cl	I	OCH$_2$CF$_3$	Et	H	Br
CH$_3$	I	OCH$_2$CF$_3$	i-Pr	H	Br	Cl	I	OCH$_2$CF$_3$	i-Pr	H	Br
CH$_3$	I	OCH$_2$CF$_3$	t-Bu	H	Br	Cl	I	OCH$_2$CF$_3$	t-Bu	H	Br
CH$_3$	I	OCH$_2$CF$_3$	Me	Me	Br	Cl	I	OCH$_2$CF$_3$	Me	Me	Br

R⁴	R⁵	R⁹	R³	R²	R⁷	R⁴	R⁵	R⁹	R³	R²	R⁷
CH₃	CF₃	CF₃	Me	H	Cl	Cl	CF₃	CF₃	Me	H	Cl
CH₃	CF₃	CF₃	Et	H	Cl	Cl	CF₃	CF₃	Et	H	Cl
CH₃	CF₃	CF₃	i-Pr	H	Cl	Cl	CF₃	CF₃	i-Pr	H	Cl
CH₃	CF₃	CF₃	t-Bu	H	Cl	Cl	CF₃	CF₃	t-Bu	H	Cl
CH₃	CF₃	CF₃	Me	Me	Cl	Cl	CF₃	CF₃	Me	Me	Cl
CH₃	CF₃	CF₃	Me	H	Br	Cl	CF₃	CF₃	Me	H	Br
CH₃	CF₃	CF₃	Et	H	Br	Cl	CF₃	CF₃	Et	H	Br
CH₃	CF₃	CF₃	i-Pr	H	Br	Cl	CF₃	CF₃	i-Pr	H	Br
CH₃	CF₃	CF₃	t-Bu	H	Br	Cl	CF₃	CF₃	t-Bu	H	Br
CH₃	CF₃	CF₃	Me	Me	Br	Cl	CF₃	CF₃	Me	Me	Br
CH₃	CF₃	Cl	Me	H	Cl	Cl	CF₃	Cl	Me	H	Cl
CH₃	CF₃	Cl	Et	H	Cl	Cl	CF₃	Cl	Et	H	Cl
CH₃	CF₃	Cl	i-Pr	H	Cl	Cl	CF₃	Cl	i-Pr	H	Cl
CH₃	CF₃	Cl	t-Bu	H	Cl	Cl	CF₃	Cl	t-Bu	H	Cl
CH₃	CF₃	Cl	Me	Me	Cl	Cl	CF₃	Cl	Me	Me	Cl
CH₃	CF₃	Cl	Me	H	Br	Cl	CF₃	Cl	Me	H	Br
CH₃	CF₃	Cl	Et	H	Br	Cl	CF₃	Cl	Et	H	Br
CH₃	CF₃	Cl	i-Pr	H	Br	Cl	CF₃	Cl	i-Pr	H	Br
CH₃	CF₃	Cl	t-Bu	H	Br	Cl	CF₃	Cl	t-Bu	H	Br
CH₃	CF₃	Cl	Me	Me	Br	Cl	CF₃	Cl	Me	Me	Br
CH₃	CF₃	Br	Me	H	Cl	Cl	CF₃	Br	Me	H	Cl
CH₃	CF₃	Br	Et	H	Cl	Cl	CF₃	Br	Et	H	Cl
CH₃	CF₃	Br	i-Pr	H	Cl	Cl	CF₃	Br	i-Pr	H	Cl
CH₃	CF₃	Br	t-Bu	H	Cl	Cl	CF₃	Br	t-Bu	H	Cl
CH₃	CF₃	Br	Me	Me	Cl	Cl	CF₃	Br	Me	Me	Cl
CH₃	CF₃	Br	Me	H	Br	Cl	CF₃	Br	Me	H	Br
CH₃	CF₃	Br	Et	H	Br	Cl	CF₃	Br	Et	H	Br
CH₃	CF₃	Br	i-Pr	H	Br	Cl	CF₃	Br	i-Pr	H	Br
CH₃	CF₃	Br	t-Bu	H	Br	Cl	CF₃	Br	t-Bu	H	Br
CH₃	CF₃	Br	Me	Me	Br	Cl	CF₃	Br	Me	Me	Br
CH₃	CF₃	OCH₂CF₃	Me	H	Cl	Cl	CF₃	OCH₂CF₃	Me	H	Cl
CH₃	CF₃	OCH₂CF₃	Et	H	Cl	Cl	CF₃	OCH₂CF₃	Et	H	Cl
CH₃	CF₃	OCH₂CF₃	i-Pr	H	Cl	Cl	CF₃	OCH₂CF₃	i-Pr	H	Cl
CH₃	CF₃	OCH₂CF₃	t-Bu	H	Cl	Cl	CF₃	OCH₂CF₃	t-Bu	H	Cl
CH₃	CF₃	OCH₂CF₃	Me	Me	Cl	Cl	CF₃	OCH₂CF₃	Me	Me	Cl
CH₃	CF₃	OCH₂CF₃	Me	H	Br	Cl	CF₃	OCH₂CF₃	Me	H	Br
CH₃	CF₃	OCH₂CF₃	Et	H	Br	Cl	CF₃	OCH₂CF₃	Et	H	Br

R⁴	R⁵	R⁹	R³	R²	R⁷	R⁴	R⁵	R⁹	R³	R²	R⁷
CH$_3$	CF$_3$	OCH$_2$CF$_3$	i-Pr	H	Br	Cl	CF$_3$	OCH$_2$CF$_3$	i-Pr	H	Br
CH$_3$	CF$_3$	OCH$_2$CF$_3$	t-Bu	H	Br	Cl	CF$_3$	OCH$_2$CF$_3$	t-Bu	H	Br
CH$_3$	CF$_3$	OCH$_2$CF$_3$	Me	Me	Br	Cl	CF$_3$	OCH$_2$CF$_3$	Me	Me	Br
CH$_3$	Cl	Cl	n-Pr	H	Cl	Cl	Cl	Cl	n-Pr	H	Cl
CH$_3$	Cl	Cl	n-Bu	H	Cl	Cl	Cl	Cl	n-Bu	H	Cl
CH$_3$	Cl	Cl	s-Bu	H	Cl	Cl	Cl	Cl	s-Bu	H	Cl
CH$_3$	Cl	Cl	i-Bu	H	Cl	Cl	Cl	Cl	i-Bu	H	Cl
CH$_3$	Cl	Cl	Et	Me	Cl	Cl	Cl	Cl	Et	Me	Cl
F	F	CF$_3$	Me	H	Cl	Br	F	CF$_3$	Me	H	Cl
F	F	CF$_3$	Et	H	Cl	Br	F	CF$_3$	Et	H	Cl
F	F	CF$_3$	i-Pr	H	Cl	Br	F	CF$_3$	i-Pr	H	Cl
F	F	CF$_3$	t-Bu	H	Cl	Br	F	CF$_3$	t-Bu	H	Cl
F	F	CF$_3$	Me	Me	Cl	Br	F	CF$_3$	Me	Me	Cl
F	F	CF$_3$	Me	H	Br	Br	F	CF$_3$	Me	H	Br
F	F	CF$_3$	Et	H	Br	Br	F	CF$_3$	Et	H	Br
F	F	CF$_3$	i-Pr	H	Br	Br	F	CF$_3$	i-Pr	H	Br
F	F	CF$_3$	t-Bu	H	Br	Br	F	CF$_3$	t-Bu	H	Br
F	F	CF$_3$	Me	Me	Br	Br	F	CF$_3$	Me	Me	Br
F	F	Cl	Me	H	Cl	Br	F	Cl	Me	H	Cl
F	F	Cl	Et	H	Cl	Br	F	Cl	Et	H	Cl
F	F	Cl	i-Pr	H	Cl	Br	F	Cl	i-Pr	H	Cl
F	F	Cl	t-Bu	H	Cl	Br	F	Cl	t-Bu	H	Cl
F	F	Cl	Me	Me	Cl	Br	F	Cl	Me	Me	Cl
F	F	Cl	Me	H	Br	Br	F	Cl	Me	H	Br
F	F	Cl	Et	H	Br	Br	F	Cl	Et	H	Br
F	F	Cl	i-Pr	H	Br	Br	F	Cl	i-Pr	H	Br
F	F	Cl	t-Bu	H	Br	Br	F	Cl	t-Bu	H	Br
F	F	Cl	Me	Me	Br	Br	F	Cl	Me	Me	Br
F	F	Br	Me	H	Cl	Br	F	Br	Me	H	Cl
F	F	Br	Et	H	Cl	Br	F	Br	Et	H	Cl
F	F	Br	i-Pr	H	Cl	Br	F	Br	i-Pr	H	Cl
F	F	Br	t-Bu	H	Cl	Br	F	Br	t-Bu	H	Cl
F	F	Br	Me	Me	Cl	Br	F	Br	Me	Me	Cl
F	F	Br	Me	H	Br	Br	F	Br	Me	H	Br
F	F	Br	Et	H	Br	Br	F	Br	Et	H	Br
F	F	Br	i-Pr	H	Br	Br	F	Br	i-Pr	H	Br
F	F	Br	t-Bu	H	Br	Br	F	Br	t-Bu	H	Br

R⁴	R⁵	R⁹	R³	R²	R⁷	R⁴	R⁵	R⁹	R³	R²	R⁷
F	F	Br	Me	Me	Br	Br	F	Br	Me	Me	Br
F	F	OCH₂CF₃	Me	H	Cl	Br	F	OCH₂CF₃	Me	H	Cl
F	F	OCH₂CF₃	Et	H	Cl	Br	F	OCH₂CF₃	Et	H	Cl
F	F	OCH₂CF₃	i-Pr	H	Cl	Br	F	OCH₂CF₃	i-Pr	H	Cl
F	F	OCH₂CF₃	t-Bu	H	Cl	Br	F	OCH₂CF₃	t-Bu	H	Cl
F	F	OCH₂CF₃	Me	Me	Cl	Br	F	OCH₂CF₃	Me	Me	Cl
F	F	OCH₂CF₃	Me	H	Br	Br	F	OCH₂CF₃	Me	H	Br
F	F	OCH₂CF₃	Et	H	Br	Br	F	OCH₂CF₃	Et	H	Br
F	F	OCH₂CF₃	i-Pr	H	Br	Br	F	OCH₂CF₃	i-Pr	H	Br
F	F	OCH₂CF₃	t-Bu	H	Br	Br	F	OCH₂CF₃	t-Bu	H	Br
F	F	OCH₂CF₃	Me	Me	Br	Br	F	OCH₂CF₃	Me	Me	Br
F	Cl	CF₃	Me	H	Cl	Br	Cl	CF₃	Me	H	Cl
F	Cl	CF₃	Et	H	Cl	Br	Cl	CF₃	Et	H	Cl
F	Cl	CF₃	i-Pr	H	Cl	Br	Cl	CF₃	i-Pr	H	Cl
F	Cl	CF₃	t-Bu	H	Cl	Br	Cl	CF₃	t-Bu	H	Cl
F	Cl	CF₃	Me	Me	Cl	Br	Cl	CF₃	Me	Me	Cl
F	Cl	CF₃	Me	H	Br	Br	Cl	CF₃	Me	H	Br
F	Cl	CF₃	Et	H	Br	Br	Cl	CF₃	Et	H	Br
F	Cl	CF₃	i-Pr	H	Br	Br	Cl	CF₃	i-Pr	H	Br
F	Cl	CF₃	t-Bu	H	Br	Br	Cl	CF₃	t-Bu	H	Br
F	Cl	CF₃	Me	Me	Br	Br	Cl	CF₃	Me	Me	Br
F	Cl	Cl	Me	H	Cl	Br	Cl	Cl	Me	H	Cl
F	Cl	Cl	Et	H	Cl	Br	Cl	Cl	Et	H	Cl
F	Cl	Cl	i-Pr	H	Cl	Br	Cl	Cl	i-Pr	H	Cl
F	Cl	Cl	t-Bu	H	Cl	Br	Cl	Cl	t-Bu	H	Cl
F	Cl	Cl	Me	Me	Cl	Br	Cl	Cl	Me	Me	Cl
F	Cl	Cl	Me	H	Br	Br	Cl	Cl	Me	H	Br
F	Cl	Cl	Et	H	Br	Br	Cl	Cl	Et	H	Br
F	Cl	Cl	i-Pr	H	Br	Br	Cl	Cl	i-Pr	H	Br
F	Cl	Cl	t-Bu	H	Br	Br	Cl	Cl	t-Bu	H	Br
F	Cl	Cl	Me	Me	Br	Br	Cl	Cl	Me	Me	Br
F	Cl	Br	Me	H	Cl	Br	Cl	Br	Me	H	Cl
F	Cl	Br	Et	H	Cl	Br	Cl	Br	Et	H	Cl
F	Cl	Br	i-Pr	H	Cl	Br	Cl	Br	i-Pr	H	Cl
F	Cl	Br	t-Bu	H	Cl	Br	Cl	Br	t-Bu	H	Cl
F	Cl	Br	Me	Me	Cl	Br	Cl	Br	Me	Me	Cl
F	Cl	Br	Me	H	Br	Br	Cl	Br	Me	H	Br

R4	R5	R9	R3	R2	R7	R4	R5	R9	R3	R2	R7
F	Cl	Br	Et	H	Br	Br	Cl	Br	Et	H	Br
F	Cl	Br	i-Pr	H	Br	Br	Cl	Br	i-Pr	H	Br
F	Cl	Br	t-Bu	H	Br	Br	Cl	Br	t-Bu	H	Br
F	Cl	Br	Me	Me	Br	Br	Cl	Br	Me	Me	Br
F	Cl	OCH2CF3	Me	H	Cl	Br	Cl	OCH2CF3	Me	H	Cl
F	Cl	OCH2CF3	Et	H	Cl	Br	Cl	OCH2CF3	Et	H	Cl
F	Cl	OCH2CF3	i-Pr	H	Cl	Br	Cl	OCH2CF3	i-Pr	H	Cl
F	Cl	OCH2CF3	t-Bu	H	Cl	Br	Cl	OCH2CF3	t-Bu	H	Cl
F	Cl	OCH2CF3	Me	Me	Cl	Br	Cl	OCH2CF3	Me	Me	Cl
F	Cl	OCH2CF3	Me	H	Br	Br	Cl	OCH2CF3	Me	H	Br
F	Cl	OCH2CF3	Et	H	Br	Br	Cl	OCH2CF3	Et	H	Br
F	Cl	OCH2CF3	i-Pr	H	Br	Br	Cl	OCH2CF3	i-Pr	H	Br
F	Cl	OCH2CF3	t-Bu	H	Br	Br	Cl	OCH2CF3	t-Bu	H	Br
F	Cl	OCH2CF3	Me	Me	Br	Br	Cl	OCH2CF3	Me	Me	Br
F	Br	CF3	Me	H	Cl	Br	Br	CF3	Me	H	Cl
F	Br	CF3	Et	H	Cl	Br	Br	CF3	Et	H	Cl
F	Br	CF3	i-Pr	H	Cl	Br	Br	CF3	i-Pr	H	Cl
F	Br	CF3	t-Bu	H	Cl	Br	Br	CF3	t-Bu	H	Cl
F	Br	CF3	Me	Me	Cl	Br	Br	CF3	Me	Me	Cl
F	Br	CF3	Me	H	Br	Br	Br	CF3	Me	H	Br
F	Br	CF3	Et	H	Br	Br	Br	CF3	Et	H	Br
F	Br	CF3	i-Pr	H	Br	Br	Br	CF3	i-Pr	H	Br
F	Br	CF3	t-Bu	H	Br	Br	Br	CF3	t-Bu	H	Br
F	Br	CF3	Me	Me	Br	Br	Br	CF3	Me	Me	Br
F	Br	Cl	Me	H	Cl	Br	Br	Cl	Me	H	Cl
F	Br	Cl	Et	H	Cl	Br	Br	Cl	Et	H	Cl
F	Br	Cl	i-Pr	H	Cl	Br	Br	Cl	i-Pr	H	Cl
F	Br	Cl	t-Bu	H	Cl	Br	Br	Cl	t-Bu	H	Cl
F	Br	Cl	Me	Me	Cl	Br	Br	Cl	Me	Me	Cl
F	Br	Cl	Me	H	Br	Br	Br	Cl	Me	H	Br
F	Br	Cl	Et	H	Br	Br	Br	Cl	Et	H	Br
F	Br	Cl	i-Pr	H	Br	Br	Br	Cl	i-Pr	H	Br
F	Br	Cl	t-Bu	H	Br	Br	Br	Cl	t-Bu	H	Br
F	Br	Cl	Me	Me	Br	Br	Br	Cl	Me	Me	Br
F	Br	Br	Me	H	Cl	Br	Br	Br	Me	H	Cl
F	Br	Br	Et	H	Cl	Br	Br	Br	Et	H	Cl
F	Br	Br	i-Pr	H	Cl	Br	Br	Br	i-Pr	H	Cl

R^4	R^5	R^9	R^3	R^2	R^7	R^4	R^5	R^9	R^3	R^2	R^7
F	Br	Br	t-Bu	H	Cl	Br	Br	Br	t-Bu	H	Cl
F	Br	Br	Me	Me	Cl	Br	Br	Br	Me	Me	Cl
F	Br	Br	Me	H	Br	Br	Br	Br	Me	H	Br
F	Br	Br	Et	H	Br	Br	Br	Br	Et	H	Br
F	Br	Br	i-Pr	H	Br	Br	Br	Br	i-Pr	H	Br
F	Br	Br	t-Bu	H	Br	Br	Br	Br	t-Bu	H	Br
F	Br	Br	Me	Me	Br	Br	Br	Br	Me	Me	Br
F	Br	OCH$_2$CF$_3$	Me	H	Cl	Br	Br	OCH$_2$CF$_3$	Me	H	Cl
F	Br	OCH$_2$CF$_3$	Et	H	Cl	Br	Br	OCH$_2$CF$_3$	Et	H	Cl
F	Br	OCH$_2$CF$_3$	i-Pr	H	Cl	Br	Br	OCH$_2$CF$_3$	i-Pr	H	Cl
F	Br	OCH$_2$CF$_3$	t-Bu	H	Cl	Br	Br	OCH$_2$CF$_3$	t-Bu	H	Cl
F	Br	OCH$_2$CF$_3$	Me	Me	Cl	Br	Br	OCH$_2$CF$_3$	Me	Me	Cl
F	Br	OCH$_2$CF$_3$	Me	H	Br	Br	Br	OCH$_2$CF$_3$	Me	H	Br
F	Br	OCH$_2$CF$_3$	Et	H	Br	Br	Br	OCH$_2$CF$_3$	Et	H	Br
F	Br	OCH$_2$CF$_3$	i-Pr	H	Br	Br	Br	OCH$_2$CF$_3$	i-Pr	H	Br
F	Br	OCH$_2$CF$_3$	t-Bu	H	Br	Br	Br	OCH$_2$CF$_3$	t-Bu	H	Br
F	Br	OCH$_2$CF$_3$	Me	Me	Br	Br	Br	OCH$_2$CF$_3$	Me	Me	Br
F	I	CF$_3$	Me	H	Cl	Br	I	CF$_3$	Me	H	Cl
F	I	CF$_3$	Et	H	Cl	Br	I	CF$_3$	Et	H	Cl
F	I	CF$_3$	i-Pr	H	Cl	Br	I	CF$_3$	i-Pr	H	Cl
F	I	CF$_3$	t-Bu	H	Cl	Br	I	CF$_3$	t-Bu	H	Cl
F	I	CF$_3$	Me	Me	Cl	Br	I	CF$_3$	Me	Me	Cl
F	I	CF$_3$	Me	H	Br	Br	I	CF$_3$	Me	H	Br
F	I	CF$_3$	Et	H	Br	Br	I	CF$_3$	Et	H	Br
F	I	CF$_3$	i-Pr	H	Br	Br	I	CF$_3$	i-Pr	H	Br
F	I	CF$_3$	t-Bu	H	Br	Br	I	CF$_3$	t-Bu	H	Br
F	I	CF$_3$	Me	Me	Br	Br	I	CF$_3$	Me	Me	Br
F	I	Cl	Me	H	Cl	Br	I	Cl	Me	H	Cl
F	I	Cl	Et	H	Cl	Br	I	Cl	Et	H	Cl
F	I	Cl	i-Pr	H	Cl	Br	I	Cl	i-Pr	H	Cl
F	I	Cl	t-Bu	H	Cl	Br	I	Cl	t-Bu	H	Cl
F	I	Cl	Me	Me	Cl	Br	I	Cl	Me	Me	Cl
F	I	Cl	Me	H	Br	Br	I	Cl	Me	H	Br
F	I	Cl	Et	H	Br	Br	I	Cl	Et	H	Br
F	I	Cl	i-Pr	H	Br	Br	I	Cl	i-Pr	H	Br
F	I	Cl	t-Bu	H	Br	Br	I	Cl	t-Bu	H	Br
F	I	Cl	Me	Me	Br	Br	I	Cl	Me	Me	Br

R4	R5	R9	R3	R2	R7	R4	R5	R9	R3	R2	R7
F	I	Br	Me	H	Cl	Br	I	Br	Me	H	Cl
F	I	Br	Et	H	Cl	Br	I	Br	Et	H	Cl
F	I	Br	i-Pr	H	Cl	Br	I	Br	i-Pr	H	Cl
F	I	Br	t-Bu	H	Cl	Br	I	Br	t-Bu	H	Cl
F	I	Br	Me	Me	Cl	Br	I	Br	Me	Me	Cl
F	I	Br	Me	H	Br	Br	I	Br	Me	H	Br
F	I	Br	Et	H	Br	Br	I	Br	Et	H	Br
F	I	Br	i-Pr	H	Br	Br	I	Br	i-Pr	H	Br
F	I	Br	t-Bu	H	Br	Br	I	Br	t-Bu	H	Br
F	I	Br	Me	Me	Br	Br	I	Br	Me	Me	Br
F	I	OCH2CF3	Me	H	Cl	Br	I	OCH2CF3	Me	H	Cl
F	I	OCH2CF3	Et	H	Cl	Br	I	OCH2CF3	Et	H	Cl
F	I	OCH2CF3	i-Pr	H	Cl	Br	I	OCH2CF3	i-Pr	H	Cl
F	I	OCH2CF3	t-Bu	H	Cl	Br	I	OCH2CF3	t-Bu	H	Cl
F	I	OCH2CF3	Me	Me	Cl	Br	I	OCH2CF3	Me	Me	Cl
F	I	OCH2CF3	Me	H	Br	Br	I	OCH2CF3	Me	H	Br
F	I	OCH2CF3	Et	H	Br	Br	I	OCH2CF3	Et	H	Br
F	I	OCH2CF3	i-Pr	H	Br	Br	I	OCH2CF3	i-Pr	H	Br
F	I	OCH2CF3	t-Bu	H	Br	Br	I	OCH2CF3	t-Bu	H	Br
F	I	OCH2CF3	Me	Me	Br	Br	I	OCH2CF3	Me	Me	Br
F	CF3	CF3	Me	H	Cl	Br	CF3	CF3	Me	H	Cl
F	CF3	CF3	Et	H	Cl	Br	CF3	CF3	Et	H	Cl
F	CF3	CF3	i-Pr	H	Cl	Br	CF3	CF3	i-Pr	H	Cl
F	CF3	CF3	t-Bu	H	Cl	Br	CF3	CF3	t-Bu	H	Cl
F	CF3	CF3	Me	Me	Cl	Br	CF3	CF3	Me	Me	Cl
F	CF3	CF3	Me	H	Br	Br	CF3	CF3	Me	H	Br
F	CF3	CF3	Et	H	Br	Br	CF3	CF3	Et	H	Br
F	CF3	CF3	i-Pr	H	Br	Br	CF3	CF3	i-Pr	H	Br
F	CF3	CF3	t-Bu	H	Br	Br	CF3	CF3	t-Bu	H	Br
F	CF3	CF3	Me	Me	Br	Br	CF3	CF3	Me	Me	Br
F	CF3	Cl	Me	H	Cl	Br	CF3	Cl	Me	H	Cl
F	CF3	Cl	Et	H	Cl	Br	CF3	Cl	Et	H	Cl
F	CF3	Cl	i-Pr	H	Cl	Br	CF3	Cl	i-Pr	H	Cl
F	CF3	Cl	t-Bu	H	Cl	Br	CF3	Cl	t-Bu	H	Cl
F	CF3	Cl	Me	Me	Cl	Br	CF3	Cl	Me	Me	Cl
F	CF3	Cl	Me	H	Br	Br	CF3	Cl	Me	H	Br
F	CF3	Cl	Et	H	Br	Br	CF3	Cl	Et	H	Br

R4	R5	R9	R3	R2	R7	R4	R5	R9	R3	R2	R7
F	CF3	Cl	i-Pr	H	Br	Br	CF3	Cl	i-Pr	H	Br
F	CF3	Cl	t-Bu	H	Br	Br	CF3	Cl	t-Bu	H	Br
F	CF3	Cl	Me	Me	Br	Br	CF3	Cl	Me	Me	Br
F	CF3	Br	Me	H	Cl	Br	CF3	Br	Me	H	Cl
F	CF3	Br	Et	H	Cl	Br	CF3	Br	Et	H	Cl
F	CF3	Br	i-Pr	H	Cl	Br	CF3	Br	i-Pr	H	Cl
F	CF3	Br	t-Bu	H	Cl	Br	CF3	Br	t-Bu	H	Cl
F	CF3	Br	Me	Me	Cl	Br	CF3	Br	Me	Me	Cl
F	CF3	Br	Me	H	Br	Br	CF3	Br	Me	H	Br
F	CF3	Br	Et	H	Br	Br	CF3	Br	Et	H	Br
F	CF3	Br	i-Pr	H	Br	Br	CF3	Br	i-Pr	H	Br
F	CF3	Br	t-Bu	H	Br	Br	CF3	Br	t-Bu	H	Br
F	CF3	Br	Me	Me	Br	Br	CF3	Br	Me	Me	Br
F	CF3	OCH2CF3	Me	H	Cl	Br	CF3	OCH2CF3	Me	H	Cl
F	CF3	OCH2CF3	Et	H	Cl	Br	CF3	OCH2CF3	Et	H	Cl
F	CF3	OCH2CF3	i-Pr	H	Cl	Br	CF3	OCH2CF3	i-Pr	H	Cl
F	CF3	OCH2CF3	t-Bu	H	Cl	Br	CF3	OCH2CF3	t-Bu	H	Cl
F	CF3	OCH2CF3	Me	Me	Cl	Br	CF3	OCH2CF3	Me	Me	Cl
F	CF3	OCH2CF3	Me	H	Br	Br	CF3	OCH2CF3	Me	H	Br
F	CF3	OCH2CF3	Et	H	Br	Br	CF3	OCH2CF3	Et	H	Br
F	CF3	OCH2CF3	i-Pr	H	Br	Br	CF3	OCH2CF3	i-Pr	H	Br
F	CF3	OCH2CF3	t-Bu	H	Br	Br	CF3	OCH2CF3	t-Bu	H	Br
F	CF3	OCH2CF3	Me	Me	Br	Br	CF3	OCH2CF3	Me	Me	Br
CH3	F	OCHF2	Me	H	Cl	Cl	F	OCHF2	Me	H	Cl
CH3	F	OCHF2	Et	H	Cl	Cl	F	OCHF2	Et	H	Cl
CH3	F	OCHF2	i-Pr	H	Cl	Cl	F	OCHF2	i-Pr	H	Cl
CH3	F	OCHF2	t-Bu	H	Cl	Cl	F	OCHF2	t-Bu	H	Cl
CH3	F	OCHF2	Me	Me	Cl	Cl	F	OCHF2	Me	Me	Cl
CH3	F	OCHF2	Me	H	Br	Cl	F	OCHF2	Me	H	Br
CH3	F	OCHF2	Et	H	Br	Cl	F	OCHF2	Et	H	Br
CH3	F	OCHF2	i-Pr	H	Br	Cl	F	OCHF2	i-Pr	H	Br
CH3	F	OCHF2	t-Bu	H	Br	Cl	F	OCHF2	t-Bu	H	Br
CH3	F	OCHF2	Me	Me	Br	Cl	F	OCHF2	Me	Me	Br
CH3	Cl	OCHF2	Me	H	Cl	Cl	Cl	OCHF2	Me	H	Cl
CH3	Cl	OCHF2	Et	H	Cl	Cl	Cl	OCHF2	Et	H	Cl
CH3	Cl	OCHF2	i-Pr	H	Cl	Cl	Cl	OCHF2	i-Pr	H	Cl
CH3	Cl	OCHF2	t-Bu	H	Cl	Cl	Cl	OCHF2	t-Bu	H	Cl

R^4	R^5	R^9	R^3	R^2	R^7	R^4	R^5	R^9	R^3	R^2	R^7
CH_3	Cl	$OCHF_2$	Me	Me	Cl	Cl	Cl	$OCHF_2$	Me	Me	Cl
CH_3	Cl	$OCHF_2$	Me	H	Br	Cl	Cl	$OCHF_2$	Me	H	Br
CH_3	Cl	$OCHF_2$	Et	H	Br	Cl	Cl	$OCHF_2$	Et	H	Br
CH_3	Cl	$OCHF_2$	i-Pr	H	Br	Cl	Cl	$OCHF_2$	i-Pr	H	Br
CH_3	Cl	$OCHF_2$	t-Bu	H	Br	Cl	Cl	$OCHF_2$	t-Bu	H	Br
CH_3	Cl	$OCHF_2$	Me	Me	Br	Cl	Cl	$OCHF_2$	Me	Me	Br
CH_3	Br	$OCHF_2$	Me	H	Cl	Cl	Br	$OCHF_2$	Me	H	Cl
CH_3	Br	$OCHF_2$	Et	H	Cl	Cl	Br	$OCHF_2$	Et	H	Cl
CH_3	Br	$OCHF_2$	i-Pr	H	Cl	Cl	Br	$OCHF_2$	i-Pr	H	Cl
CH_3	Br	$OCHF_2$	t-Bu	H	Cl	Cl	Br	$OCHF_2$	t-Bu	H	Cl
CH_3	Br	$OCHF_2$	Me	Me	Cl	Cl	Br	$OCHF_2$	Me	Me	Cl
CH_3	Br	$OCHF_2$	Me	H	Br	Cl	Br	$OCHF_2$	Me	H	Br
CH_3	Br	$OCHF_2$	Et	H	Br	Cl	Br	$OCHF_2$	Et	H	Br
CH_3	Br	$OCHF_2$	i-Pr	H	Br	Cl	Br	$OCHF_2$	i-Pr	H	Br
CH_3	Br	$OCHF_2$	t-Bu	H	Br	Cl	Br	$OCHF_2$	t-Bu	H	Br
CH_3	Br	$OCHF_2$	Me	Me	Br	Cl	Br	$OCHF_2$	Me	Me	Br
CH_3	I	$OCHF_2$	Me	H	Cl	Cl	I	$OCHF_2$	Me	H	Cl
CH_3	I	$OCHF_2$	Et	H	Cl	Cl	I	$OCHF_2$	Et	H	Cl
CH_3	I	$OCHF_2$	i-Pr	H	Cl	Cl	I	$OCHF_2$	i-Pr	H	Cl
CH_3	I	$OCHF_2$	t-Bu	H	Cl	Cl	I	$OCHF_2$	t-Bu	H	Cl
CH_3	I	$OCHF_2$	Me	Me	Cl	Cl	I	$OCHF_2$	Me	Me	Cl
CH_3	I	$OCHF_2$	Me	H	Br	Cl	I	$OCHF_2$	Me	H	Br
CH_3	I	$OCHF_2$	Et	H	Br	Cl	I	$OCHF_2$	Et	H	Br
CH_3	I	$OCHF_2$	i-Pr	H	Br	Cl	I	$OCHF_2$	i-Pr	H	Br
CH_3	I	$OCHF_2$	t-Bu	H	Br	Cl	I	$OCHF_2$	t-Bu	H	Br
CH_3	I	$OCHF_2$	Me	Me	Br	Cl	I	$OCHF_2$	Me	Me	Br
CH_3	CF_3	$OCHF_2$	Me	H	Cl	Cl	CF_3	$OCHF_2$	Me	H	Cl
CH_3	CF_3	$OCHF_2$	Et	H	Cl	Cl	CF_3	$OCHF_2$	Et	H	Cl
CH_3	CF_3	$OCHF_2$	i-Pr	H	Cl	Cl	CF_3	$OCHF_2$	i-Pr	H	Cl
CH_3	CF_3	$OCHF_2$	t-Bu	H	Cl	Cl	CF_3	$OCHF_2$	t-Bu	H	Cl
CH_3	CF_3	$OCHF_2$	Me	Me	Cl	Cl	CF_3	$OCHF_2$	Me	Me	Cl
CH_3	CF_3	$OCHF_2$	Me	H	Br	Cl	CF_3	$OCHF_2$	Me	H	Br
CH_3	CF_3	$OCHF_2$	Et	H	Br	Cl	CF_3	$OCHF_2$	Et	H	Br
CH_3	CF_3	$OCHF_2$	i-Pr	H	Br	Cl	CF_3	$OCHF_2$	i-Pr	H	Br
CH_3	CF_3	$OCHF_2$	t-Bu	H	Br	Cl	CF_3	$OCHF_2$	t-Bu	H	Br
CH_3	CF_3	$OCHF_2$	Me	Me	Br	Cl	CF_3	$OCHF_2$	Me	Me	Br
F	F	$OCHF_2$	Me	H	Cl	Br	F	$OCHF_2$	Me	H	Cl

R⁴	R⁵	R⁹	R³	R²	R⁷	R⁴	R⁵	R⁹	R³	R²	R⁷
F	F	$OCHF_2$	Et	H	Cl	Br	F	$OCHF_2$	Et	H	Cl
F	F	$OCHF_2$	i-Pr	H	Cl	Br	F	$OCHF_2$	i-Pr	H	Cl
F	F	$OCHF_2$	t-Bu	H	Cl	Br	F	$OCHF_2$	t-Bu	H	Cl
F	F	$OCHF_2$	Me	Me	Cl	Br	F	$OCHF_2$	Me	Me	Cl
F	F	$OCHF_2$	Me	H	Br	Br	F	$OCHF_2$	Me	H	Br
F	F	$OCHF_2$	Et	H	Br	Br	F	$OCHF_2$	Et	H	Br
F	F	$OCHF_2$	i-Pr	H	Br	Br	F	$OCHF_2$	i-Pr	H	Br
F	F	$OCHF_2$	t-Bu	H	Br	Br	F	$OCHF_2$	t-Bu	H	Br
F	F	$OCHF_2$	Me	Me	Br	Br	F	$OCHF_2$	Me	Me	Br
F	Cl	$OCHF_2$	Me	H	Cl	Br	Cl	$OCHF_2$	Me	H	Cl
F	Cl	$OCHF_2$	Et	H	Cl	Br	Cl	$OCHF_2$	Et	H	Cl
F	Cl	$OCHF_2$	i-Pr	H	Cl	Br	Cl	$OCHF_2$	i-Pr	H	Cl
F	Cl	$OCHF_2$	t-Bu	H	Cl	Br	Cl	$OCHF_2$	t-Bu	H	Cl
F	Cl	$OCHF_2$	Me	Me	Cl	Br	Cl	$OCHF_2$	Me	Me	Cl
F	Cl	$OCHF_2$	Me	H	Br	Br	Cl	$OCHF_2$	Me	H	Br
F	Cl	$OCHF_2$	Et	H	Br	Br	Cl	$OCHF_2$	Et	H	Br
F	Cl	$OCHF_2$	i-Pr	H	Br	Br	Cl	$OCHF_2$	i-Pr	H	Br
F	Cl	$OCHF_2$	t-Bu	H	Br	Br	Cl	$OCHF_2$	t-Bu	H	Br
F	Cl	$OCHF_2$	Me	Me	Br	Br	Cl	$OCHF_2$	Me	Me	Br
F	Br	$OCHF_2$	Me	H	Cl	Br	Br	$OCHF_2$	Me	H	Cl
F	Br	$OCHF_2$	Et	H	Cl	Br	Br	$OCHF_2$	Et	H	Cl
F	Br	$OCHF_2$	i-Pr	H	Cl	Br	Br	$OCHF_2$	i-Pr	H	Cl
F	Br	$OCHF_2$	t-Bu	H	Cl	Br	Br	$OCHF_2$	t-Bu	H	Cl
F	Br	$OCHF_2$	Me	Me	Cl	Br	Br	$OCHF_2$	Me	Me	Cl
F	Br	$OCHF_2$	Me	H	Br	Br	Br	$OCHF_2$	Me	H	Br
F	Br	$OCHF_2$	Et	H	Br	Br	Br	$OCHF_2$	Et	H	Br
F	Br	$OCHF_2$	i-Pr	H	Br	Br	Br	$OCHF_2$	i-Pr	H	Br
F	Br	$OCHF_2$	t-Bu	H	Br	Br	Br	$OCHF_2$	t-Bu	H	Br
F	Br	$OCHF_2$	Me	Me	Br	Br	Br	$OCHF_2$	Me	Me	Br
F	I	$OCHF_2$	Me	H	Cl	Br	I	$OCHF_2$	Me	H	Cl
F	I	$OCHF_2$	Et	H	Cl	Br	I	$OCHF_2$	Et	H	Cl
F	I	$OCHF_2$	i-Pr	H	Cl	Br	I	$OCHF_2$	i-Pr	H	Cl
F	I	$OCHF_2$	t-Bu	H	Cl	Br	I	$OCHF_2$	t-Bu	H	Cl
F	I	$OCHF_2$	Me	Me	Cl	Br	I	$OCHF_2$	Me	Me	Cl
F	I	$OCHF_2$	Me	H	Br	Br	I	$OCHF_2$	Me	H	Br
F	I	$OCHF_2$	Et	H	Br	Br	I	$OCHF_2$	Et	H	Br
F	I	$OCHF_2$	i-Pr	H	Br	Br	I	$OCHF_2$	i-Pr	H	Br

R^4	R^5	R^9	R^3	R^2	R^7	R^4	R^5	R^9	R^3	R^2	R^7
F	I	OCHF$_2$	t-Bu	H	Br	Br	I	OCHF$_2$	t-Bu	H	Br
F	I	OCHF$_2$	Me	Me	Br	Br	I	OCHF$_2$	Me	Me	Br
F	CF$_3$	OCHF$_2$	Me	H	Cl	Br	CF$_3$	OCHF$_2$	Me	H	Cl
F	CF$_3$	OCHF$_2$	Et	H	Cl	Br	CF$_3$	OCHF$_2$	Et	H	Cl
F	CF$_3$	OCHF$_2$	i-Pr	H	Cl	Br	CF$_3$	OCHF$_2$	i-Pr	H	Cl
F	CF$_3$	OCHF$_2$	t-Bu	H	Cl	Br	CF$_3$	OCHF$_2$	t-Bu	H	Cl
F	CF$_3$	OCHF$_2$	Me	Me	Cl	Br	CF$_3$	OCHF$_2$	Me	Me	Cl
F	CF$_3$	OCHF$_2$	Me	H	Br	Br	CF$_3$	OCHF$_2$	Me	H	Br
F	CF$_3$	OCHF$_2$	Et	H	Br	Br	CF$_3$	OCHF$_2$	Et	H	Br
F	CF$_3$	OCHF$_2$	i-Pr	H	Br	Br	CF$_3$	OCHF$_2$	i-Pr	H	Br
F	CF$_3$	OCHF$_2$	t-Bu	H	Br	Br	CF$_3$	OCHF$_2$	t-Bu	H	Br
F	CF$_3$	OCHF$_2$	Me	Me	Br	Br	CF$_3$	OCHF$_2$	Me	Me	Br
CH$_3$	CN	CF$_3$	Me	H	Cl	Cl	CN	CF$_3$	Me	H	Cl
CH$_3$	CN	CF$_3$	Et	H	Cl	Cl	CN	CF$_3$	Et	H	Cl
CH$_3$	CN	CF$_3$	i-Pr	H	Cl	Cl	CN	CF$_3$	i-Pr	H	Cl
CH$_3$	CN	CF$_3$	t-Bu	H	Cl	Cl	CN	CF$_3$	t-Bu	H	Cl
CH$_3$	CN	CF$_3$	Me	Me	Cl	Cl	CN	CF$_3$	Me	Me	Cl
CH$_3$	CN	CF$_3$	Me	H	Br	Cl	CN	CF$_3$	Me	H	Br
CH$_3$	CN	CF$_3$	Et	H	Br	Cl	CN	CF$_3$	Et	H	Br
CH$_3$	CN	CF$_3$	i-Pr	H	Br	Cl	CN	CF$_3$	i-Pr	H	Br
CH$_3$	CN	CF$_3$	t-Bu	H	Br	Cl	CN	CF$_3$	t-Bu	H	Br
CH$_3$	CN	CF$_3$	Me	Me	Br	Cl	CN	CF$_3$	Me	Me	Br
CH$_3$	CN	Cl	Me	H	Cl	Cl	CN	Cl	Me	H	Cl
CH$_3$	CN	Cl	Et	H	Cl	Cl	CN	Cl	Et	H	Cl
CH$_3$	CN	Cl	i-Pr	H	Cl	Cl	CN	Cl	i-Pr	H	Cl
CH$_3$	CN	Cl	t-Bu	H	Cl	Cl	CN	Cl	t-Bu	H	Cl
CH$_3$	CN	Cl	Me	Me	Cl	Cl	CN	Cl	Me	Me	Cl
CH$_3$	CN	Cl	Me	H	Br	Cl	CN	Cl	Me	H	Br
CH$_3$	CN	Cl	Et	H	Br	Cl	CN	Cl	Et	H	Br
CH$_3$	CN	Cl	i-Pr	H	Br	Cl	CN	Cl	i-Pr	H	Br
CH$_3$	CN	Cl	t-Bu	H	Br	Cl	CN	Cl	t-Bu	H	Br
CH$_3$	CN	Cl	Me	Me	Br	Cl	CN	Cl	Me	Me	Br
CH$_3$	CN	Br	Me	H	Cl	Cl	CN	Br	Me	H	Cl
CH$_3$	CN	Br	Et	H	Cl	Cl	CN	Br	Et	H	Cl
CH$_3$	CN	Br	i-Pr	H	Cl	Cl	CN	Br	i-Pr	H	Cl
CH$_3$	CN	Br	t-Bu	H	Cl	Cl	CN	Br	t-Bu	H	Cl
CH$_3$	CN	Br	Me	Me	Cl	Cl	CN	Br	Me	Me	Cl

R^4	R^5	R^9	R^3	R^2	R^7	R^4	R^5	R^9	R^3	R^2	R^7
CH$_3$	CN	Br	Me	H	Br	Cl	CN	Br	Me	H	Br
CH$_3$	CN	Br	Et	H	Br	Cl	CN	Br	Et	H	Br
CH$_3$	CN	Br	i-Pr	H	Br	Cl	CN	Br	i-Pr	H	Br
CH$_3$	CN	Br	t-Bu	H	Br	Cl	CN	Br	t-Bu	H	Br
CH$_3$	CN	Br	Me	Me	Br	Cl	CN	Br	Me	Me	Br
CH$_3$	CN	OCH$_2$CF$_3$	Me	H	Cl	Cl	CN	OCH$_2$CF$_3$	Me	H	Cl
CH$_3$	CN	OCH$_2$CF$_3$	Et	H	Cl	Cl	CN	OCH$_2$CF$_3$	Et	H	Cl
CH$_3$	CN	OCH$_2$CF$_3$	i-Pr	H	Cl	Cl	CN	OCH$_2$CF$_3$	i-Pr	H	Cl
CH$_3$	CN	OCH$_2$CF$_3$	t-Bu	H	Cl	Cl	CN	OCH$_2$CF$_3$	t-Bu	H	Cl
CH$_3$	CN	OCH$_2$CF$_3$	Me	Me	Cl	Cl	CN	OCH$_2$CF$_3$	Me	Me	Cl
CH$_3$	CN	OCH$_2$CF$_3$	Me	H	Br	Cl	CN	OCH$_2$CF$_3$	Me	H	Br
CH$_3$	CN	OCH$_2$CF$_3$	Et	H	Br	Cl	CN	OCH$_2$CF$_3$	Et	H	Br
CH$_3$	CN	OCH$_2$CF$_3$	i-Pr	H	Br	Cl	CN	OCH$_2$CF$_3$	i-Pr	H	Br
CH$_3$	CN	OCH$_2$CF$_3$	t-Bu	H	Br	Cl	CN	OCH$_2$CF$_3$	t-Bu	H	Br
CH$_3$	CN	OCH$_2$CF$_3$	Me	Me	Br	Cl	CN	OCH$_2$CF$_3$	Me	Me	Br
F	CN	CF$_3$	Me	H	Cl	Br	CN	CF$_3$	Me	H	Cl
F	CN	CF$_3$	Et	H	Cl	Br	CN	CF$_3$	Et	H	Cl
F	CN	CF$_3$	i-Pr	H	Cl	Br	CN	CF$_3$	i-Pr	H	Cl
F	CN	CF$_3$	t-Bu	H	Cl	Br	CN	CF$_3$	t-Bu	H	Cl
F	CN	CF$_3$	Me	Me	Cl	Br	CN	CF$_3$	Me	Me	Cl
F	CN	CF$_3$	Me	H	Br	Br	CN	CF$_3$	Me	H	Br
F	CN	CF$_3$	Et	H	Br	Br	CN	CF$_3$	Et	H	Br
F	CN	CF$_3$	i-Pr	H	Br	Br	CN	CF$_3$	i-Pr	H	Br
F	CN	CF$_3$	t-Bu	H	Br	Br	CN	CF$_3$	t-Bu	H	Br
F	CN	CF$_3$	Me	Me	Br	Br	CN	CF$_3$	Me	Me	Br
F	CN	Cl	Me	H	Cl	Br	CN	Cl	Me	H	Cl
F	CN	Cl	Et	H	Cl	Br	CN	Cl	Et	H	Cl
F	CN	Cl	i-Pr	H	Cl	Br	CN	Cl	i-Pr	H	Cl
F	CN	Cl	t-Bu	H	Cl	Br	CN	Cl	t-Bu	H	Cl
F	CN	Cl	Me	Me	Cl	Br	CN	Cl	Me	Me	Cl
F	CN	Cl	Me	H	Br	Br	CN	Cl	Me	H	Br
F	CN	Cl	Et	H	Br	Br	CN	Cl	Et	H	Br
F	CN	Cl	i-Pr	H	Br	Br	CN	Cl	i-Pr	H	Br
F	CN	Cl	t-Bu	H	Br	Br	CN	Cl	t-Bu	H	Br
F	CN	Cl	Me	Me	Br	Br	CN	Cl	Me	Me	Br
F	CN	Br	Me	H	Cl	Br	CN	Br	Me	H	Cl
F	CN	Br	Et	H	Cl	Br	CN	Br	Et	H	Cl

R^4	R^5	R^9	R^3	R^2	R^7	R^4	R^5	R^9	R^3	R^2	R^7
F	CN	Br	i-Pr	H	Cl	Br	CN	Br	i-Pr	H	Cl
F	CN	Br	t-Bu	H	Cl	Br	CN	Br	t-Bu	H	Cl
F	CN	Br	Me	Me	Cl	Br	CN	Br	Me	Me	Cl
F	CN	Br	Me	H	Br	Br	CN	Br	Me	H	Br
F	CN	Br	Et	H	Br	Br	CN	Br	Et	H	Br
F	CN	Br	i-Pr	H	Br	Br	CN	Br	i-Pr	H	Br
F	CN	Br	t-Bu	H	Br	Br	CN	Br	t-Bu	H	Br
F	CN	Br	Me	Me	Br	Br	CN	Br	Me	Me	Br
F	CN	OCH_2CF_3	Me	H	Cl	Br	CN	OCH_2CF_3	Me	H	Cl
F	CN	OCH_2CF_3	Et	H	Cl	Br	CN	OCH_2CF_3	Et	H	Cl
F	CN	OCH_2CF_3	i-Pr	H	Cl	Br	CN	OCH_2CF_3	i-Pr	H	Cl
F	CN	OCH_2CF_3	t-Bu	H	Cl	Br	CN	OCH_2CF_3	t-Bu	H	Cl
F	CN	OCH_2CF_3	Me	Me	Cl	Br	CN	OCH_2CF_3	Me	Me	Cl
F	CN	OCH_2CF_3	Me	H	Br	Br	CN	OCH_2CF_3	Me	H	Br
F	CN	OCH_2CF_3	Et	H	Br	Br	CN	OCH_2CF_3	Et	H	Br
F	CN	OCH_2CF_3	i-Pr	H	Br	Br	CN	OCH_2CF_3	i-Pr	H	Br
F	CN	OCH_2CF_3	t-Bu	H	Br	Br	CN	OCH_2CF_3	t-Bu	H	Br
F	CN	OCH_2CF_3	Me	Me	Br	Br	CN	OCH_2CF_3	Me	Me	Br
CH_3	CN	$OCHF_2$	Me	H	Cl	Cl	CN	$OCHF_2$	Me	H	Cl
CH_3	CN	$OCHF_2$	Et	H	Cl	Cl	CN	$OCHF_2$	Et	H	Cl
CH_3	CN	$OCHF_2$	i-Pr	H	Cl	Cl	CN	$OCHF_2$	i-Pr	H	Cl
CH_3	CN	$OCHF_2$	t-Bu	H	Cl	Cl	CN	$OCHF_2$	t-Bu	H	Cl
CH_3	CN	$OCHF_2$	Me	Me	Cl	Cl	CN	$OCHF_2$	Me	Me	Cl
CH_3	CN	$OCHF_2$	Me	H	Br	Cl	CN	$OCHF_2$	Me	H	Br
CH_3	CN	$OCHF_2$	Et	H	Br	Cl	CN	$OCHF_2$	Et	H	Br
CH_3	CN	$OCHF_2$	i-Pr	H	Br	Cl	CN	$OCHF_2$	i-Pr	H	Br
CH_3	CN	$OCHF_2$	t-Bu	H	Br	Cl	CN	$OCHF_2$	t-Bu	H	Br
CH_3	CN	$OCHF_2$	Me	Me	Br	Cl	CN	$OCHF_2$	Me	Me	Br
F	CN	$OCHF_2$	Me	H	Cl	Br	CN	$OCHF_2$	Me	H	Cl
F	CN	$OCHF_2$	Et	H	Cl	Br	CN	$OCHF_2$	Et	H	Cl
F	CN	$OCHF_2$	i-Pr	H	Cl	Br	CN	$OCHF_2$	i-Pr	H	Cl
F	CN	$OCHF_2$	t-Bu	H	Cl	Br	CN	$OCHF_2$	t-Bu	H	Cl
F	CN	$OCHF_2$	Me	Me	Cl	Br	CN	$OCHF_2$	Me	Me	Cl
F	CN	$OCHF_2$	Me	H	Br	Br	CN	$OCHF_2$	Me	H	Br
F	CN	$OCHF_2$	Et	H	Br	Br	CN	$OCHF_2$	Et	H	Br
F	CN	$OCHF_2$	i-Pr	H	Br	Br	CN	$OCHF_2$	i-Pr	H	Br
F	CN	$OCHF_2$	t-Bu	H	Br	Br	CN	$OCHF_2$	t-Bu	H	Br

$\underline{R^4}$	$\underline{R^5}$	$\underline{R^9}$	$\underline{R^3}$	$\underline{R^2}$	$\underline{R^7}$	$\underline{R^4}$	$\underline{R^5}$	$\underline{R^9}$	$\underline{R^3}$	$\underline{R^2}$	$\underline{R^7}$
F	CN	$OCHF_2$	Me	Me	Br	Br	CN	$OCHF_2$	Me	Me	Br